BMJ Open

Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: Population-wide analysis in Hong Kong

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052310
Article Type:	Original research
Date Submitted by the Author:	14-Apr-2021
Complete List of Authors:	Luk, Andrea; The Chinese University of Hong Kong Faculty of Medicine, Medicine and Therapeutics Yip, Terry C.F.; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Zhang, Xinge; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Kong, Alice Pik Shan; The Chinese University of Hong Kong, Prince of Wales Hosopital Wong, Vincent Wai-Sun; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Ma, Ronald; Chinese University of Hong Kong, Medicine and Therapeutics, Prince of Wales Hospital; Chinese University of Hong Kong, Hong Kong Institute of Diabetes and Obesity Wong, Grace ; The Chinese University of Hong Kong, Department of Medicine and Therapeutics
Keywords:	COVID-19, DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: Population-wide analysis in Hong Kong

Running title

Glucose-lowering drugs and COVID-19

Authors

Andrea O.Y Luk[1,2]

Terry C.F. Yip[3]

Xinge Zhang[1]

Alice P.S Kong[1,2]

Vincent W.S Wong[3]

Ronald C.W Ma[1,2]

Grace L.H Wong[3]

*AOY Luk and YCF Yip contributed equally

Affiliation

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [2]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [3]Department of Medicine and Therapeutics, Medical Data Analytics Centre, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

Corresponding author

Grace L.H. Wong

Department of Medicine and Therapeutics

The Chinese University of Hong Kong

9/F Lui Che Woo Clinical Sciences Building

Prince of Wales Hospital

30-32 Ngan Shing Street

Shatin, New Territories

Hong Kong Special Administrative Region

People's Republic of China

Tel: 852-3505-3528

email: wonglaihung@cuhk.edu.hk

Word count: 3,289

Number of table: 3

Abstract

Background:

Diabetes predisposes to serious complications from coronavirus disease 2019 (COVID-19) but it is unclear whether background use of glucose-lowering drugs affects clinical outcome.

Methods:

Between January 2020 and February 2021, 1,220 patients with diabetes were admitted to public health facilities in Hong Kong for confirmed COVID-19. Multivariate Cox regression was used to examine the association of pre-admission use versus non-use of glucose-lowering drugs (metformin, sulphonylureas, dipeptidyl peptidase-4 [DPP-4] inhibitors, insulin) with composite clinical endpoint of intensive care unit (ICU) admission, requirement of invasive mechanical ventilation, and/or in-hospital death.

Results:

In this cohort (median age 64.7 years, 54.3% men), 60.4%, 31.6%, 16.3% and 22.4% of patients were treated with metformin, sulphonylureas, DPP-4 inhibitors and insulin before admission, respectively. In multivariate Cox regression, use of metformin and DPP-4 inhibitors was associated with reduced incidence of composite endpoint relative to non-use, with respective hazard ratios of 0.51 (95% confidence interval [CI] 0.34, 0.77, p=0.001) and 0.46 (95% CI 0.29, 0.71, p<0.001), adjusted for age, sex, diabetes duration, HbA1c, smoking, comorbidities and drugs. Insulin and sulphonylurea were correlated with increased hazards of composite endpoint.

Conclusions:

Users of metformin and DPP-4 inhibitors had fewer adverse outcome from COVID-19 compared with non-users, whereas insulin and sulphonylurea might predict a worse prognosis.

Strengths and limitations of this study

- This cohort study included over 95% of all patients with COVID-19 in Hong Kong
- Statistical methods including multivariable adjustment and propensity score weighting have been adopted to adjust for important confounders of the clinical endpoints.
- The study is an observational retrospective cohort study with inherent limitations related to unmeasured confounding.
- The study is not able to infer causality given the likelihood of confounding by indication, e.g. with respect to metformin and insulin use.
- We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

Introduction

Patients with diabetes are more likely to have serious outcome from coronavirus infections including severe acute respiratory syndrome (SARS), Middle-East respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19) (1-6). In a population-based analysis of in-hospital fatalities due to COVID-19 in the United Kingdom, type 1 diabetes and type 2 diabetes were associated with increased odds of 3.5 and 2.0 for death, adjusted for age, sex and sociodemographic factors (6). The excess deaths might be related to co-occurrence of other medical conditions such as obesity and cardiovascular diseases that are independent risk factors for adverse outcome (7-10). Furthermore, diabetes gives rise to aberrant inflammatory responses which predispose to more intense lung infiltration, cytokine storm and multiorgan failure (11). Pro-inflammatory indicators such as interleukin (IL)-6, IL-2 receptor, procalcitonin, tumour

necrosis factor (TNF)-α and C-reactive protein (CRP) levels are generally higher in patients with diabetes compared with those without diabetes (12).

Several glucose-lowering drug classes have immunomodulatory effects. Metformin activates AMP-activated protein kinase (AMPK) which in turn suppresses a number of inflammatory pathways including nuclear factor kappa B and mammalian target of rapamycin (13,14). Activation of AMPK also stabilises angiotensin converting enzyme (ACE) 2, the vasodilator effect of which improve organ blood flow and may protect against lung injury (15). Both observational cohort and randomised controlled studies reported reduced risks of pneumonia and other infections with metformin therapy (16,17). Dipeptidyl peptidase-4 (DPP-4), also known as cluster of differentiation (CD) 26, is expressed in immune cells and is implicated in the regulation of adaptive immunity (18). In a case-control study of patients with COVID-19, in-hospital treatment with sitagliptin was linked to improved survival and other measures of clinical outcome (19). However, the beneficial effects of DPP-4 inhibitors have not been supported by other studies (20-22). In a territory-wide retrospective cohort of confirmed cases of COVID-19 between January 2020 and February 2021, we investigated the association between baseline use of glucose-lowering drugs and serious clinical outcome among patients with type 2 diabetes.

Methods

Setting and patients

The Hong Kong Hospital Authority (HA) governs all public hospitals and general out-patient departments in the territory and provides care for approximately 10% of local residents (23). Since the beginning of the pandemic, all cases of COVID-19, including symptomatic cases

presented to out-patient clinics or hospitals, asymptomatic contacts of confirmed cases, and inbound travellers, were admitted to HA healthcare facilities. Clinical data including past medical diagnoses, drug prescription records, laboratory results, admission records and vital status were captured in the Clinical Data Analysis and Reporting System (CDARS), an electronic medical record system used in the Hong Kong HA. We retrieved data of all patients presented with COVID-19 who admitted between 23 January 2020 (the first case in Hong Kong) and 28 February 2021 (24). All patient data were anonymised to ensure confidentiality. Patients aged below 18 years were excluded. This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Data collection

Patients with COVID-19 were identified based on positive SARS-CoV-2 polymerase chain reaction in nasopharyngeal swab in any one of the HA laboratories (25). For each patient, we obtained demographic data (age, sex), relevant diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, drug prescription record for at least 12 months before admission, laboratory results for plasma glucose, HbA1c and lipid profile for at least 12 months before admission, as well as plasma glucose, kidney function, liver function, inflammatory markers, haematology and coagulation study on the day of admission. Progress during admission including treatment with corticosteroid, intravenous immunoglobulin, anti-viral therapy, anti-fungal therapy, antibiotic therapy, mechanical ventilation, and transfer to intensive care unit (ICU) were also retrieved. Patients were followed from the date of diagnosing COVID-19 until discharge from hospital or death. Data capture was censored on 24 April 2021.

Definition and outcome

A patient was classified to have type 2 diabetes if he or she fulfilled one or more of the following criteria within 12 months before admission: use of non-insulin glucose-lowering drugs for at least one day, continuous use of insulin for ≥28 days, HbA1c ≥6.5% in any one measurement, fasting plasma glucose ≥7.0 mmol/L in any one measurement, and/or diagnosis code of type 2 diabetes based on ICD-9-CM.

Baseline use of glucose-lowering drugs, including metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), and insulin, was identified based on prescription record of the respective drug. Patients were considered to be baseline users if a prescription record was found within 12 months before and up to the day of admission. Patients were considered to be non-users if a prescription record was not found within 12 months before admission, on the day of and during admission. We have not set a minimum exposure time to define users because patients who attended the private sector for diabetes treatment would not have any prescription records in the HA CDARS before admission, but they would have a prescription record on the day of admission indicating their pre-admission use of the drug. The proportion of patients receiving medical care in the private sector is around 10% (23).

Relevant comorbidities were identified as follows: hypertension was defined as the use of blood pressuring lowering drugs within 12 months before admission and/or ICD-9-CM code of hypertension (Supplementary Table 1); chronic kidney disease was defined as having an estimated glomerular filtration rate <60 ml/min/1.73m^2 as determined using the Chronic Kidney

Disease Epidemiology Collaboration equation within 12 months prior to admission and/or ICD-9-CM codes of kidney diseases (Supplementary Table 1); chronic liver disease, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive airway disease and cancer were defined based on ICD-9-CM codes (Supplementary Table 1). The use of ICD-9-CM codes in CDARS to identify medical conditions has been shown to be 99% accurate when referenced to clinical, laboratory, imaging and endoscopy results from the electronic medical records (26). Clinical endpoints included ICU admission, mechanical ventilation, in-hospital death, and composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death. .

Statistical analysis

Analysis was conducted using R software (4.0.0). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and categorical variables as number (percentages). Between-group comparison was conducted by chi-square test for categorical variables, Student's t-test for normally distributed continuous variables, and Kruskal-Wallis test for continuous variables with skewed distribution. Clinical characteristics were compared between users and non-users of metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), and insulin. Due to small number, use of thiazolidinediones, glucagon-like peptide-1 receptor agonists and sodium-glucose transport protein 2 inhibitors were not tested. Multivariate Cox regression was conducted to derive the hazard ratios (HRs) and 95% confidence intervals (CIs) of use versus non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin for primary and secondary clinical endpoints. The multivariate Cox model was

adjusted for age, sex, diabetes duration, smoking, HbA1c, comorbidities (history of hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, and cancer), baseline use of other glucose-lowering drugs, statins and renin-angiotensin-aldosterone system (RAAS) inhibitors, and in-hospital use of other glucose-lowering drugs. The multivariate Cox regression was limited to patients with available HbA1c measurement (n=886) in whom the latest HbA1c obtained within 12 months of hospital admission was used. The selection of variables was based on known or possible link between these variables and clinical endpoints. Due to the small proportion of patients with available data on body mass index (BMI) (9.3%), BMI was not included in the multivariate Cox regression model. In a sensitivity analysis, we generated propensity scores for glucose-lowering drug use using logistic regression model that contained age, sex, smoking, diabetes duration, comorbidities and baseline use of other glucose lowering drugs, statins and RAAS inhibitors using the overlap propensity score weighting method (27). The weights were included in the multivariate Cox models to balance the differences in patient characteristics between glucose-lowering drug use groups.

Patient and Public Involvement

There was no patient or public involvement.

Results

Baseline clinical characteristics by glucose lowering drug classes

Of 9,839 adult patients with COVID-19, 1,220 patients (12.4%) had type 2 diabetes. Patients with diabetes were older, had a male preponderance and higher frequencies of comorbidities than

those without diabetes (Supplementary Table 2). In patients with diabetes, 737 (60.4%) were treated with metformin, 385 (31.6%) with sulphonylureas, 199 (16.3%) with DPP-4 inhibitors, and 273 (22.4%) with insulin at baseline. Generally, users of each of the glucose-lowering drug class had longer diabetes duration and higher HbA1c levels than non-users of the respective drug class (Table 1). Metformin users were younger and users of insulin and DPP-4 inhibitors were older than their respective non-users, whilst no age difference was detected between users and non-users of sulphonylureas (Table 1). Coronary heart disease and heart failure were less common in metformin users and more common in insulin users when compared to their respective non-users (Table 1). Chronic kidney disease was also less common in metformin users but more prevalent among users than non-users of other glucose-lowering drug classes (Table 1).

Markers of disease severity and outcome by glucose lowering drug classes

On admission, random plasma glucose levels were higher in users than non-users of most oral glucose-lowering drugs, except for DPP-4 inhibitors (Supplementary Table 3). In addition, metformin users had higher lymphocyte count, lower alkaline phosphatase (ALP) levels and lactate dehydrogenase (LDH) levels than metformin non-users (Supplementary Table 3). Users of sulphonylureas had higher CRP levels and total white cell count, and users of DPP-4 inhibitors had higher total white cell count compared with respective non-users (Supplementary Table 3). Insulin users had higher plasma glucose levels, higher levels of most inflammatory markers including LDH, CRP, erythrocyte sedimentation rate and procalcitonin, and lower lymphocyte count than insulin non-users (Supplementary Table 3).

There were overall no differences in the proportion of patients receiving most types of anti-microbial therapy, corticosteroid and IVIG between users and non-users of metformin, sulphonylureas and DPP-4 inhibitors, with the exception of less frequent administration of antibiotics among metformin users and more frequent use of anti-fungal therapy among users of sulphonylureas and DPP-4 inhibitors (Supplementary Table 3). Insulin users were more likely to be treated with anti-microbial therapy and corticosteroid than non-users (Supplementary Table 3).

During admission, 235 patients (19.3%) developed composite primary endpoint, 187 patients (15.3%) were transferred to ICU, 110 patients (9.0%) required mechanical ventilation, and 90 patients (7.4%) died. Fewer metformin users reached composite endpoint (117.2% versus 27.6%, p=0.001 or died (4.0% versus 17.3%, p<0.001) compared with non-users (Table 2). Users of sulphonlyureas and insulin were more likely than non-users to reach composite endpoint, required ICU admission and mechanical ventilation, and insulin users were also more likely to die than non-users (Table 2). The proportion of patients developing primary or secondary endpoints were similar between users and non-users of DPP-4 inhibitors (Table 2).

Association between pre-admission use of glucose lowering drugs and clinical outcome

In multivariate Cox regression model, baseline use of metformin was associated with reduced hazards of composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death (adjusted HR 0.51 [95% CI 0.34, 0.77], p=0.001) and individual endpoints of ICU admission (adjusted HR 0.53 [95% CI 0.33, 0.86], p=0.010), mechanical ventilation (adjusted HR 0.51 [95% CI 0.27, 0.97], p=0.041) and in-hospital death (adjusted HR 0.51 [95% CI 0.27, 0.97],

p=0.039) relative to non-use (Table 3). Baseline use of DPP-4 inhibitors was associated with reduced hazards of composite endpoint (adjusted HR 0.46 [95% CI 0.29, 0.71], p<0.001) and ICU admission (adjusted HR 0.45 [95% CI 0.28, 0.74]. p=0.002) (Table 3). Use of sulphonlyureas (adjusted HR 1.55 [95% CI 1.07, 2.24], p=0.022) and insulin (adjusted HR 6.34 [95% CI 3.72, 10.78], p<0.001) were both correlated with increased hazards of composite endpoint (Table 3). Sensitivity analysis using multivariate Cox regression with propensity score weighting yielded similar findings (Supplementary Table 4).

Discussion

In a territory-wide cohort of patients with diabetes presented with COVID-19, we showed that pre-admission use of metformin and DPP-4 inhibitors was linked to reduced risks of serious outcome, whereas the use of sulphonylureas and insulin was associated with a worse prognosis Our findings corroborate and extend the results of previous studies and suggest a possible protective role of metformin and DPP-4 inhibitors against severe respiratory tract infection. The strength of our study includes the unbiased nature of the cohort as the database captured all patients with COVID-19 in Hong Kong. Both symptomatic and asymptomatic patients were admitted to healthcare facilities and their clinical data were included in the present analysis. Furthermore, the use of a universal electronic medical record for drug prescription ensures that we have accurately classified use and non-use of different glucose-lowering drug classes.

Metformin, infection and COVID-19

Several observational studies in patients hospitalised with COVID-19 reported the association between metformin use and death and other measures of adverse outcome (22, 28-31). In a

nationwide study conducted in England including 2.85 million patients with type 2 diabetes among whom 13,479 had a record of COVID-19-related deaths, those prescribed metformin had fewer deaths with adjusted HR 0.77 when compared to those not prescribed metformin (22). In another study of 6,256 patients (mean age 75 years) with either type 2 diabetes or obesity admitted with COVID-19 in the United States (U.S), metformin use was found to reduce the risk of death in women with HR 0.79 adjusted for age and comorbidities although no effect was observed in men (28). Other studies, conducted mainly in the U.S, also noted a protective effect of metformin with adjusted odds or HR ranging between 0.33 and 0.48 (29,30). However, in an analysis of 1,317 patients (mean age 70 years) with COVID-19 and diabetes in France, metformin was associated with fewer deaths in univariate but not in multivariate analysis (7). Similarly, among 1,297 patients (mean age 75 years) with diabetes hospitalised for COVID-19 in Spain, the group on metformin were less likely to die and/or require ICU admission or mechanical ventilation than non-users, but no difference was detected when the two groups were propensity matched for demographics, comorbidities and drugs (20). In the present study, we found that metformin was associated with 50% reduction in the risk of in-hospital deaths and 50% reduction in the risk of composite clinical endpoint. The inconsistency in findings between studies could be due to a number of factors, including but not limited to differences in age and disease characteristics of the patient cohorts and in the statistical methods used to examine drug effects. One of the limitations of our study is the high proportion of patients with missing information on anthropometric measures and we did not include these variables in multivariate adjustment. Furthermore, confounding by indication remained an important source of bias in our study as patients who were not prescribed metformin might have other medical conditions, for example, malnutrition, kidney or liver diseases, that contraindicated the use of metformin and

conferred a poorer prognosis from COVID-19 (32). Nonetheless, our results are in line with most other studies suggesting possible benefits of metformin, or at least no evidence of harm, in patients with type 2 diabetes afflicted by COVID-19.

The immunomodulatory action of metformin has been demonstrated in cell and animal models as well as in human studies, and is independent of the metabolic function of the drug (13). In a recent randomised control trial of 53 patients taking systemic glucocorticoid for inflammatory diseases, those assigned metformin had reduced levels of high sensitivity CRP and neutrophil counts, accompanied by lower frequencies of pneumonia and moderate-to-severe infection than the placebo arm over a 12-week period (33). In the present study, metformin users had lower LDH levels and higher lymphocyte counts on admission than non-users. In infected patients, metformin may dampen the exaggerated immune reaction to SARS-CoV-2 which is causal for the development of severe lung injury and cytokine storms associated with type 2 diabetes (11).

DPP-4 inhibitors and COVID-19

Dipeptidyl-peptidase-4 inhibitors have pleiotropic effects on the immune system and the effect of this drug class as an ancillary treatment of inflammatory diseases such as rheumatoid arthritis and viral infections have been previously examined (18). Moreover, DPP-4 is a known receptor for MERS-CoV in human.It has been speculated that DPP-4 may also mediate the entry of SARS-CoV-2, although the evidences for this are yet to be consolidated (34,35). In an Italian study of 338 patients with diabetes admitted with COVID-19, in-hospital initiation of sitagliptin reduced deaths by 56% and ICU admission by 49% (19). Another case series in Italy including 90 patients with diabetes reported fewer COVID-19-related deaths among prevalent users of

DPP-4 inhibitors adjusted for age and sex (36). In the present study, baseline use of DPP-4 inhibitors was associated with reduced risk of composite clinical endpoint although in-hospital deaths were not reduced. Notably, several observational studies did not find an association between DPP-4 inhibitors and complications from COVID-19 (20,21). In particular, in the large study conducted in England, COVID-19-related deaths occurred more frequently in patients prescribed DPP-4 inhibitors (22). Differences in statistical procedures may account for the inconsistent findings. Further studies are needed to investigate whether long-term exposure of this drug class can improve prognosis of coronavirus infection.

Insulin and COVID-19

We revealed a positive relationship between pre-admission insulin use and composite clinical outcome, driven mainly by increased hazards for ICU admission and mechanical ventilation among insulin users. Our results are consistent with several other studies suggesting that insulin use may predict a worse outcome from COVID-19 (20,37). Insulin therapy is usually initiated late in the diabetes continuum and it is very possible that the positive association between insulin use and adverse outcome was due to incomplete statistical removal of confounding by indication. In the present study, insulin users were significantly older and were more likely to have premorbid kidney and cardiovascular diseases. On admission, insulin users also had higher inflammatory markers and lower lymphocyte counts which are important severity indicators. Although insulin therapy is deemed the most appropriate glucose-lowering option during acute illnesses, high level of vigilance should be maintained in managing patients on chronic insulin therapy who have a greater likelihood of deterioration.

Sulphonylurea and COVID-19

The risk association between sulphonylureas and in-hospital death was less expected and not well explained. In Hong Kong, sulphonylureas is widely prescribed as a second-line drug after metformin. In the present cohort, the frequencies of comorbidities were mostly balanced between users and non-users of sulphonylureas with the exception of a higher prevalence of chronic kidney disease among users. Previous studies on COVID-19 did not show harm associated with sulphonylurea use. Glyburide has been shown to suppress the immune system but studies on the use of sulphonylurea with infection outcome have produced mixed results (38).

Limitations

We acknowledge the following limitations. This was an observational cohort study with inherent limitations related to unmeasured confounding. Metabolic parameters including BMI were not available in a large proportion of patients and these variables were not included in the statistical adjustment. Despite statistical efforts to adjust for comorbidities, we could not fully address residual confounding by drug indication. In this connection, our results cannot be taken to infer causality between drug use and clinical outcome. Although we have included over 95% of all patients with COVID-19 in Hong Kong, the size of our cohort was relatively small. We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

Conclusion

In this retrospective cohort of Chinese with type 2 diabetes, background use of metformin and DPP-4 inhibitors was associated with fewer complications of COVID-19, whereas insulin and sulphonylureas predicted a worse prognosis. Given the increased risk for serious infection in

patients with diabetes, drugs with off-target action in immune pathways could be further evaluated for potential new application beyond the ambit of their original indication and be harnessed for use in modifying outcome from infectious diseases.

Funding

This study has received no financial support.

Author contributions

A.O.Y.L. and T.C.F.Y. contributed to conception of the article, results interpretation, drafted the manuscript and approved the final version. G.L.H.W. contributed to conception of the article, data acquisition and approved the final version. X.Z. contributed to conception of the article, statistical analysis and approved the final version. A.P.S.L., V.W.S.W. and R.C.W.M. contributed to conception of the article and approved the final version. G.L.H.W. is the guarantor of this work, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

Andrea Luk has served as a member of advisory panel for Amgen, AstraZeneca, Boehringer Ingelheim and Sanofi and received research support from Amgen, Asia Diabetes Foundation, Bayer, Boehringer Ingelheim, Lee's Pharmaceutical, MSD, Novo Nordisk, Roche, Sanofi, Sugardown Ltd, Takeda.

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences.

Xinge Zhang has no competing interests to report.

Alice Kong has received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Merck Serono, Nestle, Novo Nordisk, Pfizer and Sanofi.

Vincent Wong has served as an advisory committee member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH and Terns; and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences and Merck. He has also received a research grant from Gilead Sciences.

Ronald Ma has received research funding from AstraZeneca, Bayer, Merck Sharp & Dohme, Novo Nordisk, Pfizer and Tricida Inc. for carrying out clinical trials, and has received speaker honorarium or consultancy in advisory boards from AstraZeneca, Bayer and Boehringer Ingelheim. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research.

Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen, as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen and Roche, and received research grant from Gilead Sciences.

Data availability statement

No additional data are available.

References

1. Assiri A, AI-Tawfiq JA, AI-Rabeeah AA, AI-Rabiah FA, AI-Hajjar S, AI-Barrak A, Flemban H, AI-Nassir WN, Balkhy HH, AI-Hakeem RF, Makhdoom HQ, Zumla AI, Memish ZA. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013;13:752-761
2. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent

predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623-628

3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720
4. Wu J, Zhang J, Sun X, Wang L, Xu Y, Zhang Y, Liu X, Dong C. Influence of diabetes melllitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. Diabetes Obes Metab 2020;22:1907-1914
5. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M; COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-1355
6. Emma B, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a while-population study. Lancet Diabetes Endocrinol 2020;8:813-822

7. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébaut JF, Thivolet C, Tramunt B, Vatier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500-1515
8. Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and Coronavirus Disease 2019. Diabetes Care 2020;43:2339-2344
9. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, Hegde AA, Drazner MH, Neeland IJ, Grodin JL. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: Results from the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation 2021;143:135-144
10. Cummings MJ, Baldwin MR, Abrams D, Jocobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, Hochman BR, Salazar-Schicchi J, Yip NH, Brodie D, O'Donnell MR. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763-1770
11. Mauvais-Jarvis F. Aging, male sex, obesity and metabolic inflammation create the perfect storm for COVID-19. Diabetes 2020;69:1857-1863

12. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diab Res Care 2020;8:e001343

13. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab 2014; 20:953-966

14. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, McNeilly AD, Balfour DJ, Savinko T, Wong AK, Viollet B, Sakamoto K, Fagerholm SC, Foretz M, Lang CC, Rena G. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119:652-665

15. Zhang J, Dong J, Martin M, He M, Gongol B, Marin TL, Chen L, Shi X, Yin Y, Shang F, Wu Y. AMP-activated protein kinase phosphorylation of angiotensin-converting enzyme 2 in endothelium mitigates pulmonary hypertension. Am J Respir Crit Care Med 2018;198:509-520

16. Liang H, Ding X, Li L, Wang T, Kan Q, Wang L, Sun T. Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Crit Care 2019;23:50

17. Zhang M, He JQ. Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis. Eur J Clin Pharmacol 2020;76:149-159

18. Shao S, Xu QQ, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacol Ther 2020;209:107503

19. Solerte SB, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, Dell'Acqua M, Ippolito E, Scaranna C, Bellante R, Galliani S, Dodesini AR, Lepore G, Geni F, Fiorina RM,

Catena E, Corsico A, Colombo R, Mirani M, De Riva C, Oleandri SE, Abdi R, Bonventre JV, Rusconi S, Folli F, Di Sabatino A, Zuccotti G, Galli M, Fiorina P. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: A multicenter, case-control, retrospective, observational study. Diabetes Care 2020;43:2999-3006

20. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD, Ayala-Gutiérrez MM, Fuentes-Jiménez F, Huerta LJ, Muñoz JA, Rubio-Rivas M, Madrazo M, Garcia MG, Montes BV, Sola JF, Ena J, Ferrer RG, Pérez CM, Ripper CJ, Lecumberri JJN, Acedo IEA, Canteli SP, Cosío SF, Martínez FA, Rodríguez BC, Pérez-Martínez P, Ramos-Rincón JM, Gómez-Huelgas R; SEMI-COVID-19 Network. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Med 2020;18:359
21. Fadini GP, Morieri ML, Longato E, Bonora BM, Pinelli S, Selmin E, Voltan G, Falaguasta D, Tresso S, Costantini G, Sparacino G, Di Camillo B, Tramontan L, Cattelan AM, Vianello A, Fioretto P, Vettor R, Avogaro A. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab 2020;22:1946-1950
22. Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, Kar P, Meace C, Sattar N, Sharp S, Wareham NJ, Weaver A, Woch E, Young B, Valabhji J. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol 2021; 9:293-303

23. Census and Statistic Department. Thematic Household Survey Report No. 50. Hong Kong SAR: Census and Statistics Department, 2013. https://www.statistics.gov.hk/pub/B11302502013XXXXB0100.pdf (Accessed date: 3 February 2021)

24. Yip TC, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut 2020 [Online ahead of print]

25. Lui GC, Yip TC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Chan HL, Hui DS, Wong GL. Significantly Lower Case-fatality Ratio of Coronavirus Disease 2019 (COVID-19) than Severe Acute Respiratory Syndrome (SARS) in Hong Kong-A Territory-Wide Cohort Study. Clin Infect Dis 2020 [Online ahead of print]

26. Wong JC, Chan HL, Tse YK, Yip TC, Wong VW, Wong GL. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. Aliment Pharmacol Ther 2017;46:1001-1010

27. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol 2019;188:250-257

28. Bramante C, Ingraham N, Murray T, Marmor S, Hoversten S, Gronski J, McNeil C, Feng R, Guzman G, Abdelwahab N, King S, Meehan T, Benson B, Pendleton K, Vojta D, Tignanelli CJ. Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. medRxiv 2020;2020.06.19.20135095

29. Lally MA, Tsoukas P, Halladay CW, O'Neill E, Gravenstein S, Rudolph JL. Metformin is associated with decreased 30-day mortality among nursing home residents infected with SARS-CoV2. J Am Med Dir Assoc 2021; 22:193-198

30. Crouse A, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. medRxiv 2020;2020.07.29.20164020

31. Do JY, Kim SW, Park JW, Cho KH, Kang SH. Is there an association between metformin use and clinical outcomes in diabetes patients with COVID-19? Diabetes Metab 2020;S1262-3636(20)30159-2 [Online ahead of print]

32. Wong GL, Wong VW, Thompson A, Jia J, Hou J, Lesmana CRA, Susilo A, Tanaka Y, Chan WK, Gane E, Ong-Go AK, Lim SG, Ahn SH, Yu ML, Piratvisuth T, Chan HL; Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. Lancet Gastroenterol Hepatol 2020;5:776-787

33. Pernicova I, Kelly S, Ajodha S, Sahdev A, Bestwick JP, Gabrovska P, Akanle O, Ajjan R, Kola B, Stadler M, Fraser W, Christ-Crain M, Grossman AB, Pitzalis C, Korbonits M. Metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. Lancet Diabetes Endocrinol 2020;8:278-291

34. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251-254

35. Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes Metab Res Rev 2020; 36:e3330

36. Mirani M, Favacchio G. Carrone F, Betella N, Biamonte E. Morenghi E, Mazziotti G, Lania AG. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: A case series from an academic hospital in Lombardy, Italy. Diabetes Care 2020;43:3042-3049

37. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiang M, Deng A, Zhang Y, Zheng L, Huang K. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care 2020;43:1399-1407

38. Koh GC, Maude RR, Schreiber MF, Limmathurotsakul D, Wiersinga WJ, Wuthiekanun V, Lee SJ, Mahavanakul W, Chaowagul W, Chierakul W, White NJ, van der Poll T, Day NP, Dougan G, Peacock SJ. Glyburide is anti-inflammatory and associated with reduced mortality in melioidosis. Clin INfect Dis 2011;52:717-725

Table 1: Clinical characteristics of patients with type 2 diabetes according to pre-admission use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
Number	737	254		385	679		199	952		273	623	
Demographics												
Age, years	65.6 (57.7, 72.6)	68.9 (61.3, 79.7)	<0.001	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656	67.0 (58.4, 75.5)	65.1 (56.8, 72.2)	0.029	68.6 (60.1, 75.6)	63.3 (55.1, 71.1)	<0.001
Men, n (%)	405 (55.0)	131 (51.6)	0.391	222 (57.7)	350 (51.5)	0.063	118 (59.3)	506 (53.2)	0.133	163 (59.7)	322 (51.7)	0.032
Ex- or current smoker	125 (17.0)	49 (19.3)	0.443	70 (18.2)	113 (16.6)	0.687	34 (17.1)	163 (17.1)	0.818	55 (20.1)	107 (17.2)	0.002
Metabolic parameters												
Diabetes duration, years	1.8 (1.4, 6.4)	1.2 (0.5, 2.5)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001	3.9 (1.5, 11.3)	1.4 (0.0, 1.9)	<0.001	5.0 (1.5, 11.5)	1.4 (0.3, 1.8)	<0.001
BMI, kg/m^2	24.1 (21.5, 27.7)	23.7 (22.2, 27.0)	0.670	24.4 (21.8, 27.8)	23.5 (21.5, 27.0)	0.382	25.0 (18.7, 27.0)	23.6 (21.6, 27.4)	0.636	22.9 (19.8, 25.9)	24.4 (22.2, 27.4)	0.051

HbA1c, %	7.3 (6.6, 8.5)	6.6 (6.1, 7.8)	<0.001	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001	7.6 (6.8, 8.9)	7.2 (6.5, 8.9)	0.027	7.8 (6.9, 9.7)	6.9 (6.4, 8.0)	<0.001
LDL-cholesterol, mmol/L	2.1 (1.7, 2.7)	2.4 (1.7, 3.0)	0.004	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081	2.0 (1.5, 2.5)	2.3 (1.7, 2.8)	<0.001	2.1 (1.6, 2.8)	2.2 (1.8, 2.8)	0.174
HDL-cholesterol, mmol/L	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	0.857	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.311	1.2 (0.9, 1.4)	1.2 (1.0, 1.5)	0.003
Triglyceride, mmol/L	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)	0.093	1.3 (1.0, 1.9)	1.4 (0.9, 2.0)	0.666	1.4 (1.0, 1.9)	1.4 (1.0, 2.0)	0.774	1.3 (1.0, 1.9)	1.4 (0.9, 2.0)	0.986
Comorbidities, n (%)												
Hypertension	465 (63.1)	144 (56.7)	0.083	267 (69.4)	329 (48.5)	<0.001	123 (61.8)	498 (52.3)	0.018	154 (56.4)	333 (53.5)	0.456
Coronary heart disease	76 (10.3)	48 (18.9)	0.001	45 (11.7)	79 (11.6)	1	30 (15.1)	96 (10.1)	0.054	43 (15.8)	66 (10.6)	0.039
Heart failure	22 (3.0)	22 (8.7)	<0.001	13 (3.4)	29 (4.3)	0.578	11 (5.5)	32 (3.4)	0.208	17 (6.2)	18 (2.9)	0.029
Cerebrovascular disease	66 (9.0)	40 (15.7)	0.004	31 (8.1)	72 (10.6)	0.213	26 (13.1)	82 (8.6)	0.068	28 (10.3)	49 (7.9)	0.296
Chronic kidney disease	144 (19.5)	96 (37.8)	<0.001	98 (25.5)	135 (19.9)	0.042	72 (36.2)	164 (17.2)	<0.001	108 (39.6)	90 (14.4)	<0.001

Chronic liver disease	26 (3.5)	17 (6.7)	0.050	16 (4.2)	27 (4.0)	1	9 (4.5)	34 (3.6)	0.661	13 (4.8)	24 (3.9)	0.655
Chronic obstructive airway disease	39 (5.3)	19 (7.5)	0.260	23 (6.0)	35 (5.2)	0.671	10 (5.0)	50 (5.3)	1	13 (4.8)	39 (6.3)	0.467
Cancer	41 (5.6)	35 (13.8)	<0.001	18 (4.7)	58 (8.5)	0.026	12 (6.0)	70 (7.4)	0.611	20 (7.3)	44 (7.1)	1
Baseline drug use, n (%)												
Metformin	737 (100.0)	0 (0.0)	<0.001	352 (91.4)	343 (50.5)	<0.001	169 (84.9)	534 (56.1)	<0.001	208 (76.2)	361 (57.9)	<0.001
Sulphonylureas	352 (47.8)	27 (10.6)	<0.001	385 (100.0)	0 (0.0)	<0.001	123 (61.8)	240 (25.2)	<0.001	120 (44.0)	165 (26.5)	<0.001
DPP-4 inhibitors	169 (22.9)	28 (11.0)	<0.001	123 (31.9)	71 (10.5)	<0.001	199 (100.0)	0 (0.0)	<0.001	99 (36.3)	64 (10.3)	<0.001
Thiazolidine-diones	84 (11.4)	6 (2.4)	<0.001	58 (15.1)	31 (4.6)	<0.001	39 (19.6)	50 (5.3)	<0.001	38 (13.9)	34 (5.5)	<0.001
SGLT-2 inhibitors	70 (9.5)	8 (3.2)	0.002	37 (9.6)	41 (6.0)	0.043	41 (20.6)	34 (3.6)	<0.001	41 (15.0)	24 (3.9)	<0.001
GLP1 receptor agonists	11 (1.5)	2 (0.8)	0.533	4 (1.0)	9 (1.3)	0.779	4 (2.0)	8 (0.8)	0.138	7 (2.6)	5 (0.8)	0.053
Insulin	208 (28.2)	49 (19.3)	0.007	120 (31.2)	129 (19.0)	<0.001	99 (49.7)	157 (16.5)	<0.001	273 (100.0)	0 (0.0)	<0.001
Statins	546 (74.1)	138 (54.3)	<0.001	294 (76.4)	379 (55.8)	<0.001	153 (76.9)	528 (55.5)	<0.001	190 (69.6)	366 (58.7)	0.003

Blood pressure lowering drugs	473 (64.2)	165 (65.0)	0.882	250 (64.9)	381 (56.1)	0.006	129 (64.8)	529 (55.6)	0.020	177 (64.8)	345 (55.4)	0.010
RAAS inhibitors	440 (59.7)	126 (49.6)	0.006	248 (64.4)	303 (44.6)	<0.001	134 (67.3)	428 (45.0)	<0.001	165 (60.4)	286 (45.9)	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HDL, high density-lipoprotein; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium glucose co-transporter-2

Table 2: Clinical outcome from COVID-19 according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
ICU admission, n (%)	108 (14.7)	43 (16.9)	0.442	79 (20.5)	79 (11.6)	<0.001	32 (16.1)	136 (14.3)	0.588	76 (27.8)	17 (2.7)	<0.001
Mechanical ventilation, n (%)	67 (9.1)	24 (9.5)	0.965	51 (13.2)	43 (6.3)	<0.001	22 (11.1)	78 (8.2)	0.244	51 (18.7)	4 (0.6)	<0.001
In-hospital death, n (%)	44 (6.0)	44 (17.3)	<0.001	35 (9.1)	47 (6.9)	0.248	18 (9.1)	71 (7.5)	0.538	32 (11.7)	22 (3.5)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	127 (17.2)	70 (27.6)	0.001	91 (23.6)	109 (16.1)	0.003	40 (20.1)	175 (18.4)	0.642	88 (32.2)	35 (5.6)	<0.001

DPP-4, dipeptidyl peptidase-4; ICU, intensive care unit

Table 3: Multivariate Cox regression for the association between baseline use of glucose lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission	0.53 (0.33, 0.86)	0.01	1.45 (0.96, 2.19)	0.074	0.45 (0.28, 0.74)	0.002	10.95 (5.5, 21.8)	<0.001
Mechanical ventilation	0.51 (0.27, 0.97)	0.041	1.35 (0.78, 2.36)	0.286	0.57 (0.29, 1.11)	0.098	21.99 (4.85, 99.6)	<0.001
In-hospital death	0.51 (0.27, 0.97)	0.039	2.42 (1.25, 4.7)	0.009	0.70 (0.35, 1.39)	0.304	2.86 (1.09, 7.48)	0.033
ICU admission, mechanical ventilation and/or in-hospital death	0.51 (0.34, 0.77)	0.001	1.55 (1.07, 2.24)	0.022	0.46 (0.29, 0.71)	<0.001	6.34 (3.72, 10.78)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), pre-admission use of other glucose-lowering drugs, statins, and RAAS inhibitors, and in-hospital use of other glucose-lowering drugs

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 1: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for comorbidities

Disease	ICD-9-CM Code	Description
Cardiovascular diseases		
Hypertension and hypertensive diseases	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive chronic kidney disease
	404	Hypertensive heart and chronic kidney disease
	405	Secondary hypertension
Coronary heart disease	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	412	Old myocardial infarction
	413	Angina pectoris
	414	Other forms of chronic ischemic heart disease
Heart failure	428	Heart failure
Chronic liver disease		
Chronic liver disease, liver failure, liver cirrhosis and complications	570	Chronic liver disease and cirrhosis
Diabetes mellitus		
Diabetes mellitus	250	Diabetes mellitus
Cancer		
Malignant neoplasm	140-149	Malignant neoplasm of lip, oral cavity, and pharynx
	150-159	Malignant neoplasm of digestive organs and peritoneum
	160-165	Malignant neoplasm of respiratory and intrathoracic organ
	170-176	Malignant neoplasm of bone, connective tissue, skin, and breast
	179-189	Malignant neoplasm of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites
	200-209	Malignant neoplasm of lymphatic and hematopoietic tissue
Cerebrovascular disease		
Cerebrovascular events	430	Subarachnoid haemorrhage
	431	Intracerebral haemorrhage
	432	Other and unspecified intracranial haemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
	438	Late effects of cerebrovascular disease
Chronic obstructive airway disease		
Chronic obstructive pulmonary disease and allied conditions	490-496	Chronic obstructive pulmonary disease and allied conditions
Kidney diseases		
Nephritis, nephrotic syndrome, and nephrosis	581	Nephrotic syndrome
	582	Chronic glomerulonephritis
	583	Nephritis and nephropathy not specified as acute or chronic
	585	Chronic kidney disease
	586	Renal failure, unspecified
	587	Renal sclerosis, unspecified
	588	Disorders resulting from impaired renal function
Others	403.1	
	403.9	Benign hypertensive renal disease
	04.12404.1	Unspecified hypertensive renal disease

3	Benign hypertensive heart and renal disease
404.1	Unspecified hypertensive heart and renal disease
404.9	Polycystic kidney, unspecified type
753.12	Polycystic kidney, autosomal dominant
753.13	Polycystic kidney, autosomal recessive
753.14	Gouty nephropathy
274.1	Postural proteinuria
593.6	Unspecified disorder of kidney and ureter
593.9	

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Supplementary Table 2: Baseline clinical characteristics and in-hospital outcome of patients with and without type 2 diabetes admitted with COVID-19 in Hong Kong between January 2020 and February 2021

	Patients with diabetes		Patients without diabetes		
	Number (%) with available data		Number (%) with available data		p-value
Demographics					
Age, years	1220 (100.0)	65.3 (57.1, 73.1)	9839 (100.0)	44.6 (32.3, 58.6)	<0.001
Men, n (%)	1220 (100.0)	662 (54.3)	9839 (100.0)	4047 (47.0)	<0.001
Ex- or current smoker	1220 (100.0)	209 (17.1)	9839 (100.0)	868 (10.1)	0.001
Metabolic parameters					
Diabetes duration, years	1220 (100.0)	1.4 (0.3, 3.4)	-	-	-
BMI, kg/m^2	114 (9.3)	23.6 (21.5, 27.3)	598 (6.1)	23.5 (20.9, 26.5)	0.380
HbA1c, %	886 (72.6)	7.4 (6.6, 9.2)	1901 (19.3)	5.8 (5.4, 6.3)	<0.001
Comorbidities, n (%)					
Hypertension	1220 (100.0)	644 (52.8)	9839 (100.0)	815 (9.5)	<0.001
Coronary heart disease	1220 (100.0)	130 (10.7)	9839 (100.0)	148 (1.7)	<0.001
Heart failure	1220 (100.0)	44 (3.6)	9839 (100.0)	44 (0.5)	<0.001
Cerebrovascular disease	1220 (100.0)	111 (9.1)	9839 (100.0)	148 (1.7)	<0.001
Chronic kidney disease	1220 (100.0)	249 (20.4)	9839 (100.0)	235 (2.7)	<0.001

Chronic liver disease	1220 (100.0)	44 (3.6)	9839 (100.0)	44 (0.5)	<0.001
Chronic obstructive airway disease	1220 (100.0)	61 (5.0)	9839 (100.0)	235 (2.7)	<0.001
Cancer	1220 (100.0)	83 (6.8)	9839 (100.0)	180 (2.1)	<0.001
Baseline drug use, n (%)					
Metformin	1220 (100.0)	737 (60.4)	9839 (100.0)	0	<0.001
Sulphonylureas	1220 (100.0)	385 (31.6)	9839 (100.0)	0	<0.001
DPP-4 inhibitors	1220 (100.0)	199 (16.3)	9839 (100.0)	0	<0.001
Thiazolidinediones	1220 (100.0)	90 (7.4)	9839 (100.0)	0	<0.001
SGLT-2 inhibitors	1220 (100.0)	78 (6.4)	9839 (100.0)	0	<0.001
GLP1 receptor agonists	1220 (100.0)	13 (1.1)	9839 (100.0)	0	0.011
Insulin	1220 (100.0)	273 (22.4)	9839 (100.0)	0	<0.001
Statins	1220 (100.0)	709 (58.1)	9839 (100.0)	572 (6.6)	<0.001
Blood pressure lowering drugs	1220 (100.0)	691 (56.6)	9839 (100.0)	1108 (12.9)	<0.001
RAAS inhibitors	1220 (100.0)	590 (48.4)	9839 (100.0)	452 (5.2)	<0.001
In-hospital treatment, n (%)					
Oseltamivir	1220 (100.0)	16 (1.3)	9839 (100.0)	63 (0.7)	0.051
Ribavirin	1220 (100.0)	396 (32.5)	9839 (100.0)	1823 (21.2)	<0.001
Lopinavir-ritonavir	1220 (100.0)	335 (27.5)	9839 (100.0)	1542 (17.9)	<0.001

Interferon beta	1220 (100.0)	725 (59.4)	9839 (100.0)	2702 (31.3)	<0.001
Antibiotic therapy	1220 (100.0)	755 (61.9)	9839 (100.0)	2769 (32.1)	<0.001
Anti-fungal therapy	1220 (100.0)	124 (10.2)	9839 (100.0)	265 (3.1)	<0.001
Corticosteroid	1220 (100.0)	623 (51.1)	9839 (100.0)	1747 (20.3)	<0.001
Pulse methylprednisolone	1220 (100.0)	5 (0.4)	9839 (100.0)	7 (0.1)	0.011
Intravenous immune globulin	1220 (100.0)	6 (0.5)	9839 (100.0)	9 (0.1)	0.007
Clinical outcome, n (%)					
ICU admission	1220 (100.0)	187 (15.3)	9839 (100.0)	269 (3.1)	<0.001
Mechanical ventilation	1220 (100.0)	110 (9.0)	9839 (100.0)	142 (1.7)	<0.001
In-hospital death	1220 (100.0)	90 (7.4)	9839 (100.0)	105 (1.2)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death	1220 (100.0)	235 (19.3)	9839 (100.0)	340 (3.9)	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HDL, high density-lipoprotein; ICU, intensive care unit; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium glucose co-transporter-2

Supplementary Table 3: Laboratory results on admission and in-hospital treatment of patients with type 2 diabetes according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
Number	737	254		385	679		199	952		273	623	
Laboratory results on admission												
Random glucose, mmol/L	8.1 (6.4, 11.0)	7.1 (6.0, 9.0)	<0.001	8.7 (6.5, 12.1)	7.5 (6.1, 9.7)	<0.001	8.7 (6.6, 11.9)	8.0 (6.4, 11.2)	0.108	9.2 (6.6, 12.8)	7.6 (6.2, 9.5)	<0.001
Sodium, mmol/L	137.0 (134.0, 139.0)	138.0 (135.0, 140.0)	0.018	137.0 (134.0, 139.0)	138.0 (135.0, 140.0)	0.001	136.0 (134.0, 139.0)	137.0 (134.0, 139.0)	0.01	136.0 (133.0, 138.0)	138.0 (136.0, 140.0)	<0.001
Potassium, mmol/L	3.9 (3.6, 4.0)	3.8 (3.5, 4.2)	0.938	3.9 (3.6, 4.3)	3.8 (3.5, 4.2)	<0.001	4.0 (3.7, 4.4)	3.8 (3.5, 4.1)	<0.001	4.0 (3.6, 4.4)	3.8 (3.5, 4.1)	<0.001
Creatinine, µmol/L	77.7 (63.0, 98.0)	83.0 (66.7, 124.0)	<0.001	81.2 (66.0, 110.0)	75.0 (62.8, 95.0)	<0.001	90.0 (70.0, 138.0)	75.0 (62.4, 94.0)	<0.001	91.3 (71.0, 140.0)	72.0 (61.0, 88.1)	<0.001
Albumin, g/L	38.4 (35.0, 41.3)	37.5 (33.0, 41.0)	0.006	38.0 (34.1, 41.0)	38.7 (34.9, 41.7)	0.076	37.0 (33.3, 41.0)	38.7 (35.0, 41.7)	0.019	36.0 (32.0, 39.4)	39.7 (36.0, 42.1)	<0.001
Total bilirubin, µmol/L	7.9 (6.0, 10.2)	8.1 (6.0, 12.0)	0.164	7.8 (6.0, 10.0)	8.0 (5.8, 11.0)	0.580	7.5 (5.4, 10.4)	8.0 (6.0, 11.0)	0.116	8.0 (5.8, 10.6)	8.0 (6.0, 10.6)	0.604
ALP, U/L	67.3 (55.1, 82.0)	74.0 (60.0, 92.4)	<0.001	70.0 (57.0, 84.0)	69.0 (56.0, 84.0)	0.752	70.0 (57.0, 83.0)	69.1 (57.0, 84.8)	0.789	69.3 (55.0, 88.0)	70.0 (57.5, 83.5)	0.843

ALT, U/L	27.0 (18.0, 39.5)	25.1 (16.9, 37.0)	0.295	27.8 (20.0, 39.4)	26.1 (17.0, 41.0)	0.142	26.0 (17.8, 34.9)	27.0 (18.0, 41.7)	0.145	24.4 (17.0, 36.0)	28.6 (19.0, 42.8)	<0.001
LDH, U/L	213.0 (178.0, 277.0)	234.0 (192.0, 303.0)	0.002	214.0 (183.0, 281.0)	219.0 (180.0, 281.0)	0.720	216.0 (190.0, 277.0)	217.0 (181.0, 283.0)	0.505	246.0 (192.0, 362.0)	209.0 (175.0, 254.0)	<0.001
CRP, mg/dL	1.3 (0.4, 4.7)	1.2 (0.3, 5.0)	0.980	1.7 (0.4, 5.4)	1.1 (0.4, 3.9)	0.032	1.5 (0.4, 5.3)	1.3 (0.4, 4.6)	0.376	2.9 (0.5, 7.5)	0.8 (0.3, 2.6)	<0.001
ESR, mm/hour	38.6 (21.0, 65.2)	47.0 (22.5, 84.1)	0.060	43.0 (20.5, 68.0)	37.0 (21.0, 64.0)	0.844	45.6 (21.5, 72.5)	39.8 (21.0, 68.0)	0.622	46.0 (25.0, 80.0)	34.0 (18.5, 53.5)	0.002
Procalcitonin, ng/mL	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.039	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.299	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.308	0.1 (0.1, 0.3)	0.1 (0.1, 0.1)	<0.001
Haemoglobin, g/dL	13.0 (12.0, 14.0)	12.9 (11.6, 14.2)	0.225	12.9 (11.8, 13.9)	13.2 (12.1, 14.3)	0.008	12.9 (11.6, 13.9)	13.2 (12.1, 14.3)	0.003	12.9 (11.5, 14.0)	13.2 (12.1, 14.2)	0.002
White cell count, $x10^9$/L	5.7 (4.6, 7.2)	5.7 (4.4, 7.2)	0.611	5.8 (4.8, 7.4)	5.6 (4.4, 7.0)	0.002	6.1 (4.6, 7.4)	5.6 (4.5, 7.1)	0.031	6.1 (4.8, 8.0)	5.5 (4.4, 6.9)	<0.001
Lymphocyte count, $x10^9$/L	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	0.044	1.2 (0.9, 1.6)	1.2 (0.8, 1.5)	0.451	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	0.138	1.1 (0.8, 1.4)	1.2 (0.9, 1.7)	<0.001
Platelet count, $x10^9$/L	204.0 (160.0, 254.0)	188.0 (149.0, 234.0)	0.003	206.0 (161.0, 258.0)	197.0 (156.0, 243.0)	0.027	204.0 (159.0, 249.0)	198.0 (156.0, 250.0)	0.336	199.0 (151.0, 255.0)	207.0 (166.0, 260.0)	0.101
Prothrombin time, seconds	11.9 (11.3, 12.5)	12.1 (11.4, 12.9)	0.006	11.9 (11.4, 12.6)	11.9 (11.3, 12.5)	0.819	12.1 (11.5, 12.8)	11.9 (11.3, 12.5)	0.026	12.1 (11.5, 12.9)	11.8 (11.2, 12.3)	<0.001
In-hospital treatment, n (%)												

Oseltamivir	9 (1.22)	2 (0.79)	0.739	5.0 (1.3)	10.0 (1.5)	1	3.0 (1.5)	11.0 (1.2)	0.72	7.0 (2.6)	6.0 (1.0)	0.074
Ribavirin	236 (32.0)	84 (33.1)	0.818	125.0 (32.5)	221.0 (32.5)	1	75.0 (37.7)	290.0 (30.5)	0.056	103.0 (37.7)	185.0 (29.7)	0.022
Lopinavir-ritonavir	200 (27.1)	73 (28.7)	0.681	110.0 (28.6)	184.0 (27.1)	0.656	53.0 (26.6)	256.0 (26.9)	1	93.0 (34.1)	125.0 (20.1)	<0.001
Interferon beta	425 (57.7)	164 (64.6)	0.063	220.0 (57.1)	409.0 (60.2)	0.357	122.0 (61.3)	556.0 (58.4)	0.498	187.0 (68.5)	309.0 (49.6)	<0.001
Antibiotic therapy	444 (60.2)	176 (69.3)	0.013	246.0 (63.9)	405.0 (59.6)	0.193	125.0 (62.8)	582.0 (61.1)	0.717	210.0 (76.9)	273.0 (43.8)	<0.001
Anti-fungal therapy	80 (10.9)	26 (10.2)	0.875	52.0 (13.5)	58.0 (8.5)	0.014	32.0 (16.1)	81.0 (8.5)	0.002	47.0 (17.2)	40.0 (6.4)	<0.001
Corticosteroid	367 (49.8)	142 (55.9)	0.108	201.0 (52.2)	330.0 (48.6)	0.286	108.0 (54.3)	475.0 (49.9)	0.296	168.0 (61.5)	203.0 (32.6)	<0.001
Pulse methylprednisolone	2 (0.27)	1 (0.39)	1	1.0 (0.3)	4.0 (0.6)	0.659	0.0 (0.0)	4.0 (0.4)	1	1.0 (0.4)	1.0 (0.2)	0.517
IVIG	2 (0.27)	2 (0.79)	0.272	2.0 (0.5)	2.0 (0.3)	0.623	0.0 (0.0)	5.0 (0.5)	0.594	2.0 (0.7)	0.0 (0.0)	0.093

Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables

ALP, alkaline phosphatase; ALT, alanine transaminase; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; ESR, erythrocyte sedimentation rate; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase

Supplementary Table 4: Multivariate Cox regression with propensity score weighting for the association between baseline use of glucose-lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission, n (%)	0.51 (0.30, 0.86)	0.012	1.42 (0.90, 2.25)	0.131	0.46 (0.28, 0.76)	0.002	9.79 (4.26, 22.50)	<0.001
Mechanical ventilation, n (%)	0.29 (0.12, 0.72)	0.008	1.30 (0.70, 2.44)	0.405	0.42 (0.18, 0.98)	0.044	21.21 (4.40, 102.31)	<0.001
In-hospital death, n (%)	0.45 (0.23, 0.89)	0.022	2.87 (1.40, 5.88)	0.004	0.78 (0.38, 1.59)	0.487	2.86 (0.81, 10.13)	0.103
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	0.53 (0.35, 0.81)	0.003	1.55 (1.02, 2.34)	0.04	0.48 (0.30, 0.76)	0.002	5.90 (3.41, 10.20)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), baseline use of other glucose-lowering drugs, statins and RAAS inhibitors, in-hospital use of other glucose-lowering drugs, and propensity score

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10, 25-26
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: Population-wide analysis in Hong Kong

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052310.R1
Article Type:	Original research
Date Submitted by the Author:	14-Sep-2021
Complete List of Authors:	Luk, Andrea; The Chinese University of Hong Kong Faculty of Medicine, Medicine and Therapeutics Yip, Terry C.F.; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Zhang, Xinge; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Kong, Alice Pik Shan; The Chinese University of Hong Kong, Prince of Wales Hosopital Wong, Vincent Wai-Sun; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Ma, Ronald; Chinese University of Hong Kong, Medicine and Therapeutics, Prince of Wales Hospital; Chinese University of Hong Kong, Hong Kong Institute of Diabetes and Obesity Wong, Grace ; The Chinese University of Hong Kong, Department of Medicine and Therapeutics
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Infectious diseases
Keywords:	COVID-19, DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: Population-wide analysis in Hong Kong

Running title

Glucose-lowering drugs and COVID-19

Authors

Andrea O.Y Luk[1,2]

Terry C.F. Yip[3]

Xinge Zhang[1]

Alice P.S Kong[1,2]

Vincent W.S Wong[3]

Ronald C.W Ma[1,2]

Grace L.H Wong[3]

*AOY Luk and YCF Yip contributed equally

Affiliation

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [2]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [3]Department of Medicine and Therapeutics, Medical Data Analytics Centre, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

Corresponding author

Grace L.H. Wong

Department of Medicine and Therapeutics

The Chinese University of Hong Kong

9/F Lui Che Woo Clinical Sciences Building

Prince of Wales Hospital

30-32 Ngan Shing Street

Shatin, New Territories

Hong Kong Special Administrative Region

People's Republic of China

Tel: 852-3505-3528

email: wonglaihung@cuhk.edu.hk

Word count: 3,489

Number of table: 3

Abstract

Objectives: Diabetes predisposes to serious complications from coronavirus disease 2019 (COVID-19) but it is unclear whether background use of glucose-lowering drugs affects clinical outcome.

Setting: all public health facilities in Hong Kong

Participants: 1,220 patients with diabetes who were admitted for confirmed COVID-19

Primary and secondary outcome measures: composite clinical endpoint of intensive care unit (ICU) admission, requirement of invasive mechanical ventilation, and/or in-hospital death.

Results: In this cohort (median age 64.7 years, 54.3% men), 60.4%, 31.6%, 16.3% and 22.4% of patients were treated with metformin, sulphonylureas, DPP-4 inhibitors and insulin before admission, respectively. In multivariate Cox regression, use of metformin and DPP-4 inhibitors was associated with reduced incidence of composite endpoint relative to non-use, with respective hazard ratios of 0.51 (95% confidence interval [CI] 0.34, 0.77, p=0.001) and 0.46 (95% CI 0.29, 0.71, p<0.001), adjusted for age, sex, diabetes duration, HbA1c, smoking, comorbidities and drugs. Insulin and sulphonylurea were correlated with increased hazards of composite endpoint.

Conclusions: Users of metformin and DPP-4 inhibitors had fewer adverse outcome from COVID-19 compared with non-users, whereas insulin and sulphonylurea might predict a worse prognosis.

Strengths and limitations of this study

- This cohort study included over 95% of all patients with COVID-19 in Hong Kong
- Statistical methods including multivariable adjustment and propensity score weighting have been adopted to adjust for important confounders of the clinical endpoints.
- The study is an observational retrospective cohort study with inherent limitations related to unmeasured confounding.
- The study is not able to infer causality given the likelihood of confounding by indication, e.g. with respect to metformin and insulin use.
- We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

Introduction

Patients with diabetes are more likely to have serious outcome from coronavirus infections including severe acute respiratory syndrome (SARS), Middle-East respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19) (1-6). In a population-based analysis of in-hospital fatalities due to COVID-19 in the United Kingdom, type 1 diabetes and type 2 diabetes were associated with increased odds of 3.5 and 2.0 for death, adjusted for age, sex and sociodemographic factors (6). The excess deaths might be related to co-occurrence of other medical conditions such as obesity and cardiovascular diseases that are independent risk factors for adverse outcome (7-10). Furthermore, diabetes gives rise to aberrant inflammatory responses which predispose to more intense lung infiltration, cytokine storm and multiorgan failure (11). Pro-inflammatory indicators such as interleukin (IL)-6, IL-2 receptor, procalcitonin, tumour necrosis factor (TNF)-α and C-reactive protein (CRP) levels are generally higher in patients with diabetes compared with those without diabetes (12).

Several glucose-lowering drug classes have immunomodulatory effects. Metformin activates AMP-activated protein kinase (AMPK) which in turn suppresses a number of inflammatory pathways including nuclear factor kappa B and mammalian target of rapamycin (13,14). Activation of AMPK also stabilises angiotensin converting enzyme (ACE) 2, the vasodilator effect of which improve organ blood flow and may protect against lung injury (15). Both observational cohort and randomised controlled studies reported reduced risks of pneumonia and other infections with metformin therapy (16,17). Dipeptidyl peptidase-4 (DPP-4), also known as cluster of differentiation (CD) 26, is expressed in immune cells and is implicated in the

regulation of adaptive immunity (18). In a case-control study of patients with COVID-19, in-hospital treatment with sitagliptin was linked to improved survival and other measures of clinical outcome (19). However, the beneficial effects of DPP-4 inhibitors have not been supported by other studies (20-22). In a territory-wide retrospective cohort of confirmed cases of COVID-19 between January 2020 and February 2021, we investigated the association between baseline use of glucose-lowering drugs and serious clinical outcome among patients with type 2 diabetes.

Methods

Setting and patients

The Hong Kong Hospital Authority (HA) governs all public hospitals and general out-patient departments in the territory and provides care for approximately 80% of local residents (23). Given the high cost differential in healthcare between the public and private sector with the private sector being significantly more expensive, people who utilise health services in the private sector are usually at a more favourable socioeconomic position. Since the beginning of the pandemic, all cases of COVID-19, including symptomatic cases presented to out-patient clinics or hospitals, asymptomatic contacts of confirmed cases, and inbound travellers, were admitted to HA healthcare facilities. Clinical data including past medical diagnoses, drug prescription records, laboratory results, admission records and vital status were captured in the Clinical Data Analysis and Reporting System (CDARS), an electronic medical record system used in the Hong Kong HA. We retrieved data of all patients presented with COVID-19 who admitted between 23 January 2020 (the first case in Hong Kong) and 28 February 2021 (24). All patient data were anonymised to ensure confidentiality. Patients aged below 18 years were

excluded. This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Data collection

Patients with COVID-19 were identified based on positive SARS-CoV-2 polymerase chain reaction in nasopharyngeal swab in any one of the HA laboratories (25). For each patient, we obtained demographic data (age, sex), relevant diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, drug prescription record for at least 12 months before admission, laboratory results for plasma glucose, HbA1c and lipid profile for at least 12 months before admission, as well as plasma glucose, kidney function, liver function, inflammatory markers, haematology and coagulation study on the day of admission. Progress during admission including treatment with corticosteroid, intravenous immunoglobulin, anti-viral therapy, anti-fungal therapy, antibiotic therapy, mechanical ventilation, and transfer to intensive care unit (ICU) were also retrieved. Patients were followed from the date of diagnosing COVID-19 until discharge from hospital or death. Data capture was censored on 24 April 2021.

Definition and outcome

A patient was classified to have type 2 diabetes if he or she fulfilled one or more of the following criteria within 12 months before admission: use of non-insulin glucose-lowering drugs for at least one day, continuous use of insulin for ≥28 days, HbA1c ≥6.5% in any one measurement, fasting plasma glucose ≥7.0 mmol/L in any one measurement, and/or diagnosis code of type 2 diabetes based on ICD-9-CM.

Baseline use of glucose-lowering drugs, including metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), and insulin, was identified based on prescription record of the respective drug. Patients were considered to be baseline users if a prescription record was found within 12 months before and up to the day of admission. Patients were considered to be non-users if a prescription record was not found within 12 months before admission, on the day of and during admission. We have not set a minimum exposure time to define users because patients who attended the private sector for diabetes treatment would not have any prescription records in the HA CDARS before admission, but they would have a prescription record on the day of admission indicating their pre-admission use of the drug. The proportion of patients receiving medical care in the private sector is around 10% (23).

Relevant comorbidities were identified as follows: hypertension was defined as the use of blood pressuring lowering drugs within 12 months before admission and/or ICD-9-CM code of hypertension (Supplementary Table 1); chronic kidney disease was defined as having an estimated glomerular filtration rate <60 ml/min/1.73m^2 as determined using the Chronic Kidney Disease Epidemiology Collaboration equation within 12 months prior to admission and/or ICD-9-CM codes of kidney diseases (Supplementary Table 1); chronic liver disease, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive airway disease and cancer were defined based on ICD-9-CM codes (Supplementary Table 1). The use of ICD-9-CM codes in CDARS to identify medical conditions has been shown to be 99% accurate when referenced to clinical, laboratory, imaging and endoscopy results from the electronic medical records (26). Clinical endpoints included ICU admission, mechanical ventilation, in-hospital

death, and composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death. For the composite endpoint, patients were followed from the date of diagnosing COVID-19 until the date of ICU admission, use of mechanical ventilation, in-hospital death, or discharge from hospital, whichever came first. For the individual clinical endpoint, patients were followed from the date of diagnosing COVID-19 until the date of the occurrence of that individual clinical endpoint or discharge from hospital, whichever came first.

Statistical analysis

Analysis was conducted using R software (4.0.0). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and categorical variables as number (percentages). Between-group comparison was conducted by chi-square test for categorical variables, Student's t-test for normally distributed continuous variables, and Kruskal-Wallis test for continuous variables with skewed distribution. Clinical characteristics were compared between users and non-users of metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), and insulin. Due to small number, use of thiazolidinediones, glucagon-like peptide-1 receptor agonists and sodium-glucose transport protein 2 inhibitors were not tested. Multivariate Cox regression was conducted to derive the hazard ratios (HRs) and 95% confidence intervals (CIs) of use versus non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin for primary and secondary clinical endpoints. The multivariate Cox model was adjusted for age, sex, diabetes duration, smoking, HbA1c, comorbidities (history of hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, and cancer), baseline

use of other glucose-lowering drugs, statins and renin-angiotensin-aldosterone system (RAAS) inhibitors, and in-hospital use of other glucose-lowering drugs. The multivariate Cox regression was limited to patients with available HbA1c measurement (n=886) in whom the latest HbA1c obtained within 12 months of hospital admission was used. The selection of variables was based on known or possible link between these variables and clinical endpoints. Due to the small proportion of patients with available data on body mass index (BMI) (9.3%), BMI was not included in the multivariate Cox regression model. In a sensitivity analysis, we generated propensity scores for glucose-lowering drug use using logistic regression model that contained age, sex, smoking, diabetes duration, comorbidities and baseline use of other glucose lowering drugs, statins and RAAS inhibitors using the overlap propensity score weighting method (27). The weights were included in the multivariate Cox models to balance the differences in patient characteristics between glucose-lowering drug use groups. We also repeated the multivariate Cox regression excluding patients whose diabetes status was established by a single fasting plasma glucose measurement only, as these patients might not have diabetes.

Patient and Public Involvement

There was no patient of public involvement.

Results

Baseline clinical characteristics by glucose lowering drug classes

Of 9,839 adult patients with COVID-19, 1,220 patients (12.4%) had type 2 diabetes. Patients with diabetes were older, had a male preponderance and higher frequencies of comorbidities than those without diabetes (Supplementary Table 2). In patients with diabetes, 737 (60.4%) were

treated with metformin, 385 (31.6%) with sulphonylureas, 199 (16.3%) with DPP-4 inhibitors, and 273 (22.4%) with insulin at baseline. Generally, users of each of the glucose-lowering drug class had longer diabetes duration and higher HbA1c levels than non-users of the respective drug class (Table 1). Metformin users were younger and users of insulin and DPP-4 inhibitors were older than their respective non-users, whilst no age difference was detected between users and non-users of sulphonylureas (Table 1). Coronary heart disease and heart failure were less common in metformin users and more common in insulin users when compared to their respective non-users (Table 1). Chronic kidney disease was also less common in metformin users but more prevalent among users than non-users of other glucose-lowering drug classes (Table 1).

Markers of disease severity and outcome by glucose lowering drug classes

On admission, random plasma glucose levels were higher in users than non-users of most oral glucose-lowering drugs, except for DPP-4 inhibitors (Supplementary Table 3). In addition, metformin users had higher lymphocyte count, lower alkaline phosphatase (ALP) levels and lactate dehydrogenase (LDH) levels than metformin non-users (Supplementary Table 3). Users of sulphonylureas had higher CRP levels and total white cell count, and users of DPP-4 inhibitors had higher total white cell count compared with respective non-users (Supplementary Table 3). Insulin users had higher plasma glucose levels, higher levels of most inflammatory markers including LDH, CRP, erythrocyte sedimentation rate and procalcitonin, and lower lymphocyte count than insulin non-users (Supplementary Table 3).

There were overall no differences in the proportion of patients receiving most types of anti-microbial therapy, corticosteroid and IVIG between users and non-users of metformin,

sulphonylureas and DPP-4 inhibitors, with the exception of less frequent administration of antibiotics among metformin users and more frequent use of anti-fungal therapy among users of sulphonylureas and DPP-4 inhibitors (Supplementary Table 3). Insulin users were more likely to be treated with anti-microbial therapy and corticosteroid than non-users (Supplementary Table 3).

During admission, 235 patients (19.3%) developed composite primary endpoint, 187 patients (15.3%) were transferred to ICU, 110 patients (9.0%) required mechanical ventilation, and 90 patients (7.4%) died. Fewer metformin users reached composite endpoint (Proportions: 17.2% versus 27.6%, p=0.001; Incidence rates: 4914.1 versus 6633.4 per 1,000 person-year, p=0.043) or died (Proportions: 4.0% versus 17.3%, p<0.001; Incidence rates: 1258.8 versus 2946.5 per 1,000 person-year, p<0.001) compared with non-users (Table 2, Supplementary Table 4). Users of sulphonlyureas and insulin were more likely than non-users to reach composite endpoint, required ICU admission and mechanical ventilation, and insulin users were also more likely to die than non-users (Table 2, Supplementary Table 4). The proportion of patients developing primary or secondary endpoints were similar between users and non-users of DPP-4 inhibitors (Table 2, Supplementary Table 4).

Association between pre-admission use of glucose lowering drugs and clinical outcome

In multivariate Cox regression model, baseline use of metformin was associated with reduced hazards of composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death (adjusted HR 0.51 [95% CI 0.34, 0.77], p=0.001) and individual endpoints of ICU admission (adjusted HR 0.53 [95% CI 0.33, 0.86], p=0.010), mechanical ventilation (adjusted HR 0.51

[95% CI 0.27, 0.97], p=0.041) and in-hospital death (adjusted HR 0.51 [95% CI 0.27, 0.97], p=0.039) relative to non-use (Table 3). Baseline use of DPP-4 inhibitors was associated with reduced hazards of composite endpoint (adjusted HR 0.46 [95% CI 0.29, 0.71], p<0.001) and ICU admission (adjusted HR 0.45 [95% CI 0.28, 0.74]. p=0.002) (Table 3). Use of sulphonlyureas (adjusted HR 1.55 [95% CI 1.07, 2.24], p=0.022) and insulin (adjusted HR 6.34 [95% CI 3.72, 10.78], p<0.001) were both correlated with increased hazards of composite endpoint (Table 3). Sensitivity analysis using multivariate Cox regression with propensity score weighting yielded similar findings (Supplementary Table 5). Exclusion of patients who were identified as having diabetes based on a single fasting plasma glucose measurement (n=25) had minimal effect on the results (Supplementary Table 6).

Discussion

In a territory-wide cohort of patients with diabetes presented with COVID-19, we showed that pre-admission use of metformin and DPP-4 inhibitors was linked to reduced risks of serious outcome, whereas the use of sulphonylureas and insulin was associated with a worse prognosis Our findings corroborate and extend the results of previous studies and suggest a possible protective role of metformin and DPP-4 inhibitors against severe respiratory tract infection. The strength of our study includes the unbiased nature of the cohort as the database captured all patients with COVID-19 in Hong Kong. Both symptomatic and asymptomatic patients were admitted to healthcare facilities and their clinical data were included in the present analysis. Furthermore, the use of a universal electronic medical record for drug prescription ensures that we have accurately classified use and non-use of different glucose-lowering drug classes.

Metformin, infection and COVID-19

Several observational studies in patients hospitalised with COVID-19 reported the association between metformin use and death and other measures of adverse outcome (22, 28-31). In a nationwide study conducted in England including 2.85 million patients with type 2 diabetes among whom 13,479 had a record of COVID-19-related deaths, those prescribed metformin had fewer deaths with adjusted HR 0.77 when compared to those not prescribed metformin (22). In another study of 6,256 patients (mean age 75 years) with either type 2 diabetes or obesity admitted with COVID-19 in the United States (U.S), metformin use was found to reduce the risk of death in women with HR 0.79 adjusted for age and comorbidities although no effect was observed in men (28). Two meta-analyses also noted a protective effect of metformin with pooled odds ratios of around 0.6 for mortality from COVID-19 (32,33). However, in an analysis of 1,317 patients (mean age 70 years) with COVID-19 and diabetes in France, metformin was associated with fewer deaths in univariate but not in multivariate analysis (7). Similarly, among 1,297 patients (mean age 75 years) with diabetes hospitalised for COVID-19 in Spain, the group on metformin were less likely to die and/or require ICU admission or mechanical ventilation than non-users, but no difference was detected when the two groups were propensity matched for demographics, comorbidities and drugs (20). In the present study, we found that metformin was associated with 50% reduction in the risk of in-hospital deaths and 50% reduction in the risk of composite clinical endpoint. The inconsistency in findings between studies could be due to a number of factors, including but not limited to differences in age and disease characteristics of the patient cohorts and in the statistical methods used to examine drug effects. One of the limitations of our study is the high proportion of patients with missing information on anthropometric measures and we did not include these variables in multivariate adjustment.

Furthermore, confounding by indication remained an important source of bias in our study as patients who were not prescribed metformin might have other medical conditions, for example, malnutrition, kidney or liver diseases, that contraindicated the use of metformin and conferred a poorer prognosis from COVID-19 (34). Nonetheless, our results are in line with most other studies suggesting possible benefits of metformin, or at least no evidence of harm, in patients with type 2 diabetes afflicted by COVID-19.

The immunomodulatory action of metformin has been demonstrated in cell and animal models as well as in human studies, and is independent of the metabolic function of the drug (13). In a recent randomised control trial of 53 patients taking systemic glucocorticoid for inflammatory diseases, those assigned metformin had reduced levels of high sensitivity CRP and neutrophil counts, accompanied by lower frequencies of pneumonia and moderate-to-severe infection than the placebo arm over a 12-week period (35). In the present study, metformin users had lower LDH levels and higher lymphocyte counts on admission than non-users. In infected patients, metformin may dampen the exaggerated immune reaction to SARS-CoV-2 which is causal for the development of severe lung injury and cytokine storms associated with type 2 diabetes (11).

DPP-4 inhibitors and COVID-19

Dipeptidyl-peptidase-4 inhibitors have pleiotropic effects on the immune system and the effect of this drug class as an ancillary treatment of inflammatory diseases such as rheumatoid arthritis and viral infections have been previously examined (18). Moreover, DPP-4 is a known receptor for MERS-CoV in human. It has been speculated that DPP-4 may also mediate the entry of SARS-CoV-2, although the evidences for this are yet to be consolidated (36,37). In an Italian

study of 338 patients with diabetes admitted with COVID-19, in-hospital initiation of sitagliptin reduced deaths by 56% and ICU admission by 49% (19). Another case series in Italy including 90 patients with diabetes reported fewer COVID-19-related deaths among prevalent users of DPP-4 inhibitors adjusted for age and sex (38). In the present study, baseline use of DPP-4 inhibitors was associated with reduced risk of composite clinical endpoint although in-hospital deaths were not reduced. Notably, several observational studies and a meta-analysis did not find an association between DPP-4 inhibitors and complications from COVID-19 (20,21,39). In particular, in the large study conducted in England, COVID-19-related deaths occurred more frequently in patients prescribed DPP-4 inhibitors (22). Differences in statistical procedures may account for the inconsistent findings. Further studies are needed to investigate whether long-term exposure of this drug class can improve prognosis of coronavirus infection.

Insulin and COVID-19

We revealed a positive relationship between pre-admission insulin use and composite clinical outcome, driven mainly by increased hazards for ICU admission and mechanical ventilation among insulin users. Our results are consistent with several other studies suggesting that insulin use may predict a worse outcome from COVID-19 (20,40). Insulin therapy is usually initiated late in the diabetes continuum and it is very possible that the positive association between insulin use and adverse outcome was due to incomplete statistical removal of confounding by indication. In the present study, insulin users were significantly older and were more likely to have premorbid kidney and cardiovascular diseases. On admission, insulin users also had higher inflammatory markers and lower lymphocyte counts which are important severity indicators. Although insulin therapy is deemed the most appropriate glucose-lowering option during acute

illnesses, high level of vigilance should be maintained in managing patients on chronic insulin therapy who have a greater likelihood of deterioration.

Sulphonylurea and COVID-19

The risk association between sulphonylureas and in-hospital death was less expected and not well explained. In Hong Kong, sulphonylureas is widely prescribed as a second-line drug after metformin. In the present cohort, the frequencies of comorbidities were mostly balanced between users and non-users of sulphonylureas with the exception of a higher prevalence of chronic kidney disease among users. Previous studies on COVID-19 did not show harm associated with sulphonylurea use. Glyburide has been shown to suppress the immune system but studies on the use of sulphonylurea with infection outcome have produced mixed results (41).

Limitations

We acknowledge the following limitations. This was an observational cohort study with inherent limitations related to unmeasured confounding. Metabolic parameters including BMI were not available in a large proportion of patients and these variables were not included in the statistical adjustment. Despite statistical efforts to adjust for comorbidities, we could not fully address residual confounding by drug indication. In this connection, our results cannot be taken to infer causality between drug use and clinical outcome. Although we have included over 95% of all patients with COVID-19 in Hong Kong, the size of our cohort was relatively small. We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

Conclusion

In this retrospective cohort of Chinese with type 2 diabetes, background use of metformin and DPP-4 inhibitors was associated with fewer complications of COVID-19, whereas insulin and sulphonylureas predicted a worse prognosis. Given the increased risk for serious infection in patients with diabetes, drugs with off-target action in immune pathways could be further evaluated for potential new application beyond the ambit of their original indication and be harnessed for use in modifying outcome from infectious diseases.

Funding

This study has received no financial support.

Author contributions

A.O.Y.L. and T.C.F.Y. contributed to conception of the article, results interpretation, drafted the manuscript and approved the final version. G.L.H.W. contributed to conception of the article, data acquisition and approved the final version. X.Z. contributed to conception of the article, statistical analysis and approved the final version. A.P.S.L., V.W.S.W. and R.C.W.M. contributed to conception of the article and approved the final version. G.L.H.W. is the guarantor of this work, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

Andrea Luk has served as a member of advisory panel for Amgen, AstraZeneca, Boehringer Ingelheim and Sanofi and received research support from Amgen, Asia Diabetes Foundation,

Bayer, Boehringer Ingelheim, Lee's Pharmaceutical, MSD, Novo Nordisk, Roche, Sanofi, Sugardown Ltd, Takeda.

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences.

Xinge Zhang has no competing interests to report.

Alice Kong has received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Merck Serono, Nestle, Novo Nordisk, Pfizer and Sanofi.

Vincent Wong has served as an advisory committee member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH and Terns; and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences and Merck. He has also received a research grant from Gilead Sciences.

Ronald Ma has received research funding from AstraZeneca, Bayer, Merck Sharp & Dohme, Novo Nordisk, Pfizer and Tricida Inc. for carrying out clinical trials, and has received speaker honorarium or consultancy in advisory boards from AstraZeneca, Bayer and Boehringer Ingelheim. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research.

Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen, as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen and Roche, and received research grant from Gilead Sciences.

Data availability statement

No additional data are available.

Ethics Statement

This study involves human participants and was approved by an Ethics Committee(s) or Institutional Board(s) - The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (the Joint CUHK-NTEC CREC) (Reference number: 2021.239).

References

1. Assiri A, AI-Tawfiq JA, AI-Rabeeah AA, AI-Rabiah FA, AI-Hajjar S, AI-Barrak A, Flemban H, AI-Nassir WN, Balkhy HH, AI-Hakeem RF, Makhdoom HQ, Zumla AI, Memish ZA. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013;13:752-761
2. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623-628
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720

4. Wu J, Zhang J, Sun X, Wang L, Xu Y, Zhang Y, Liu X, Dong C. Influence of diabetes melllitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. Diabetes Obes Metab 2020;22:1907-1914

5. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M; COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-1355

6. Emma B, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a while-population study. Lancet Diabetes Endocrinol 2020;8:813-822

7. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébaut JF, Thivolet C, Tramunt B, Vatier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500-1515

8. Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and Coronavirus Disease 2019. Diabetes Care 2020;43:2339-2344
9. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, Hegde AA, Drazner MH, Neeland IJ, Grodin JL. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: Results from the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation 2021;143:135-144
10. Cummings MJ, Baldwin MR, Abrams D, Jocobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, Hochman BR, Salazar-Schicchi J, Yip NH, Brodie D, O'Donnell MR. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763-1770
11. Mauvais-Jarvis F. Aging, male sex, obesity and metabolic inflammation create the perfect storm for COVID-19. Diabetes 2020;69:1857-1863
12. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diab Res Care 2020;8:e001343
13. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab 2014; 20:953-966
14. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, McNeilly AD, Balfour DJ, Savinko T, Wong AK, Viollet B, Sakamoto K, Fagerholm SC, Foretz M,

Lang CC, Rena G. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119:652-665

15. Zhang J, Dong J, Martin M, He M, Gongol B, Marin TL, Chen L, Shi X, Yin Y, Shang F, Wu Y. AMP-activated protein kinase phosphorylation of angiotensin-converting enzyme 2 in endothelium mitigates pulmonary hypertension. Am J Respir Crit Care Med 2018;198:509-520
16. Liang H, Ding X, Li L, Wang T, Kan Q, Wang L, Sun T. Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Crit Care 2019;23:50
17. Zhang M, He JQ. Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis. Eur J Clin Pharmacol 2020;76:149-159
18. Shao S, Xu QQ, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacol Ther 2020;209:107503
19. Solerte SB, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, Dell'Acqua M, Ippolito E, Scaranna C, Bellante R, Galliani S, Dodesini AR, Lepore G, Geni F, Fiorina RM, Catena E, Corsico A, Colombo R, Mirani M, De Riva C, Oleandri SE, Abdi R, Bonventre JV, Rusconi S, Folli F, Di Sabatino A, Zuccotti G, Galli M, Fiorina P. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: A multicenter, case-control, retrospective, observational study. Diabetes Care 2020;43:2999-3006
20. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD, Ayala-Gutiérrez MM, Fuentes-Jiménez F, Huerta LJ, Muñoz JA, Rubio-Rivas M, Madrazo M, Garcia MG,

Montes BV, Sola JF, Ena J, Ferrer RG, Pérez CM, Ripper CJ, Lecumberri JJN, Acedo IEA, Canteli SP, Cosío SF, Martínez FA, Rodríguez BC, Pérez-Martínez P, Ramos-Rincón JM, Gómez-Huelgas R; SEMI-COVID-19 Network. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Med 2020;18:359

21. Fadini GP, Morieri ML, Longato E, Bonora BM, Pinelli S, Selmin E, Voltan G, Falaguasta D, Tresso S, Costantini G, Sparacino G, Di Camillo B, Tramontan L, Cattelan AM, Vianello A, Fioretto P, Vettor R, Avogaro A. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab 2020;22:1946-1950
22. Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, Kar P, Meace C, Sattar N, Sharp S, Wareham NJ, Weaver A, Woch E, Young B, Valabhji J. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol 2021; 9:293-303
23. Census and Statistic Department. Thematic Household Survey Report No. 50. Hong Kong SAR: Census and Statistics Department, 2013. https://www.statistics.gov.hk/pub/B11302502013XXXXB0100.pdf (Accessed date: 3 February 2021)
24. Yip TC, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut 2020 [Online ahead of print]

25. Lui GC, Yip TC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Chan HL, Hui DS, Wong GL. Significantly Lower Case-fatality Ratio of Coronavirus Disease 2019 (COVID-19) than Severe Acute Respiratory Syndrome (SARS) in Hong Kong-A Territory-Wide Cohort Study. Clin Infect Dis 2020 [Online ahead of print]

26. Wong JC, Chan HL, Tse YK, Yip TC, Wong VW, Wong GL. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. Aliment Pharmacol Ther 2017;46:1001-1010

27. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol 2019;188:250-257

28. Bramante C, Ingraham N, Murray T, Marmor S, Hoversten S, Gronski J, McNeil C, Feng R, Guzman G, Abdelwahab N, King S, Meehan T, Benson B, Pendleton K, Vojta D, Tignanelli CJ. Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. medRxiv 2020;2020.06.19.20135095

29. Lally MA, Tsoukas P, Halladay CW, O'Neill E, Gravenstein S, Rudolph JL. Metformin is associated with decreased 30-day mortality among nursing home residents infected with SARS-CoV2. J Am Med Dir Assoc 2021; 22:193-198

30. Crouse A, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. medRxiv 2020;2020.07.29.20164020

31. Do JY, Kim SW, Park JW, Cho KH, Kang SH. Is there an association between metformin use and clinical outcomes in diabetes patients with COVID-19? Diabetes Metab 2020;S1262-3636(20)30159-2 [Online ahead of print]

32. Henrina J, Lim MA, Lawrensia S, Suastika K. The effect of metformin consumption on mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab Syndr 2020; 14:2177-2183

33. Kow CS, Hasan SS. Mortality risk with preadmission metformin use in patients with COVID-19 and diabetes: A meta-analysis. J Med Virol 2021; 93:695-697

34. Wong GL, Wong VW, Thompson A, Jia J, Hou J, Lesmana CRA, Susilo A, Tanaka Y, Chan WK, Gane E, Ong-Go AK, Lim SG, Ahn SH, Yu ML, Piratvisuth T, Chan HL; Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. Lancet Gastroenterol Hepatol 2020;5:776-787

35. Pernicova I, Kelly S, Ajodha S, Sahdev A, Bestwick JP, Gabrovska P, Akanle O, Ajjan R, Kola B, Stadler M, Fraser W, Christ-Crain M, Grossman AB, Pitzalis C, Korbonits M. Metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. Lancet Diabetes Endocrinol 2020;8:278-291

36. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251-254

37. Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes Metab Res Rev 2020; 36:e3330

38. Mirani M, Favacchio G. Carrone F, Betella N, Biamonte E. Morenghi E, Mazziotti G, Lania AG. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4

inhibitors in patients with type 2 diabetes with COVID-19: A case series from an academic hospital in Lombardy, Italy. Diabetes Care 2020;43:3042-3049

39. Hariyanto TI, Kurniawan A. Dipeptidyl peptidase 4 (DPP4) inhibitor and outcome from coronavirus disease 2019 (COVID-19) in diabetic patients: a systematic review, meta-analysis, and meta-regression. J Diabetes Metab Disord 2021; 20:1-8
40. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiang M, Deng A, Zhang Y, Zheng L, Huang K. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care 2020;43:1399-1407
41. Koh GC, Maude RR, Schreiber MF, Limmathurotsakul D, Wiersinga WJ, Wuthiekanun V, Lee SJ, Mahavanakul W, Chaowagul W, Chierakul W, White NJ, van der Poll T, Day NP, Dougan G, Peacock SJ. Glyburide is anti-inflammatory and associated with reduced mortality in melioidosis. Clin INfect Dis 2011;52:717-725

Table 1: Clinical characteristics of patients with type 2 diabetes according to pre-admission use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin.

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	*P*	Users	Non-users	*P*	Users	Non-users	*P*	Users	Non-users	*P*
Number	737	254		385	679		199	952		385	679	
Demographics												
Age, years	65.6 (57.7, 72.6)	68.9 (61.3, 79.7)	<0.001	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656	67.0 (58.4, 75.5)	65.1 (56.8, 72.2)	0.029	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656
Men, n (%)	405 (55.0)	131 (51.6)	0.391	222 (57.7)	350 (51.5)	0.063	118 (59.3)	506 (53.2)	0.133	222 (57.7)	350 (51.5)	0.063
Ex-/active smoker, n (%)	125 (17.0)	49 (19.3)	0.443	70 (18.2)	113 (16.6)	0.687	34 (17.1)	163 (17.1)	0.818	70 (18.2)	113 (16.6)	0.687
Metabolic parameters												
Diabetes duration, years	1.8 (1.4, 6.4)	1.2 (0.5, 2.5)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001	3.9 (1.5, 11.3)	1.4 (0.0, 1.9)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001
HbA1c, %	7.3 (6.6, 8.5)	6.6 (6.1, 7.8)	<0.001	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001	7.6 (6.8, 8.9)	7.2 (6.5, 8.9)	0.027	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001
LDL-C, mmol/L	2.1 (1.7, 2.7)	2.4 (1.7, 3.0)	0.004	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081	2.0 (1.5, 2.5)	2.3 (1.7, 2.8)	<0.001	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081
HDL-C, mmol/L	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	0.857	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.311	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17
Triglyceride, mmol/L	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)	0.093	1.3 (1.0, 1.9)	1.36 (0.9, 2.0)	0.666	1.4 (1.0, 1.9)	1.4 (1.0, 2.0)	0.774	1.3 (1.0, 1.9)	1.36 (0.9, 2.0)	0.666
Comorbidities, n (%)												
Hypertension	465 (63.1)	144 (56.7)	0.083	267 (69.4)	329 (48.5)	<0.001	123 (61.8)	498 (52.3)	0.018	267 (69.4)	329 (48.5)	<0.001
Coronary heart disease	76 (10.3)	48 (18.9)	0.001	45 (11.7)	79 (11.6)	1	30 (15.1)	96 (10.1)	0.054	45 (11.7)	79 (11.6)	1
Heart failure	22 (3.0)	22 (8.7)	<0.001	13 (3.4)	29 (4.3)	0.578	11 (5.5)	32 (3.4)	0.208	13 (3.4)	29 (4.3)	0.578
Cerebrovascular disease	66 (9.0)	40 (15.7)	0.004	31 (8.1)	72 (10.6)	0.213	26 (13.1)	82 (8.6)	0.068	31 (8.1)	72 (10.6)	0.213
Chronic kidney disease	144 (19.5)	96 (37.8)	<0.001	98 (25.5)	135 (19.9)	0.042	72 (36.2)	164 (17.2)	<0.001	98 (25.5)	135 (19.9)	0.042
Chronic liver disease	26 (3.5)	17 (6.7)	0.05	16 (4.2)	27 (4.0)	1	9 (4.5)	34 (3.6)	0.661	16 (4.2)	27 (4.0)	1
COPD	39 (5.3)	19 (7.5)	0.26	23 (6.0)	35 (5.2)	0.671	10 (5.0)	50 (5.3)	1	23 (6.0)	35 (5.2)	0.671
Cancer	41 (5.6)	35 (13.8)	<0.001	18 (4.7)	58 (8.5)	0.026	12 (6.0)	70 (7.4)	0.611	18 (4.7)	58 (8.5)	0.026
Baseline drug use, n (%)												
Metformin	737 (100.0)	0 (0.0)	<0.001	352 (91.4)	343 (50.5)	<0.001	169 (84.9)	534 (56.1)	<0.001	352 (91.4)	343 (50.5)	<0.001
Sulphonylureas	352 (47.8)	27 (10.6)	<0.001	385 (100.0)	0 (0.0)	<0.001	123 (61.8)	240 (25.2)	<0.001	385 (100.0)	0 (0.0)	<0.001

DPP-4 inhibitors	169 (22.9)	28 (11.0)	<0.001	123 (31.9)	71 (10.5)	<0.001	199 (100.0)	0 (0.0)	<0.001	123 (31.9)	71 (10.5)	<0.001
Thiazolidine-diones	84 (11.4)	6 (2.4)	<0.001	58 (15.1)	31 (4.6)	<0.001	39 (19.6)	50 (5.3)	<0.001	58 (15.1)	31 (4.6)	<0.001
SGLT-2 inhibitors	70 (9.5)	8 (3.2)	0.002	37 (9.6)	41 (6.0)	0.043	41 (20.6)	34 (3.6)	<0.001	37 (9.6)	41 (6.0)	0.043
GLP1 receptor agonists	11 (1.5)	2 (0.8)	0.533	4 (1.0)	9 (1.3)	0.779	4 (2.0)	8 (0.8)	0.138	4 (1.0)	9 (1.3)	0.779
Insulin	208 (28.2)	49 (19.3)	0.007	120 (31.2)	129 (19.0)	<0.001	99 (49.7)	157 (16.5)	<0.001	120 (31.2)	129 (19.0)	<0.001
Statins	546 (74.1)	138 (54.3)	<0.001	294 (76.4)	379 (55.8)	<0.001	153 (76.9)	528 (55.5)	<0.001	294 (76.4)	379 (55.8)	<0.001
BP lowering drugs	473 (64.2)	165 (65.0)	0.882	250 (64.9)	381 (56.1)	0.006	129 (64.8)	529 (55.6)	0.02	250 (64.9)	381 (56.1)	0.006
RAAS inhibitors	440 (59.7)	126 (49.6)	0.006	248 (64.4)	303 (44.6)	<0.001	134 (67.3)	428 (45.0)	<0.001	248 (64.4)	303 (44.6)	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI, body mass index; BP, blood pressure; COPD, chronic obstructive airway disease; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HDL-C, high density-lipoprotein cholesterol; LDL-C, low density-lipoprotein cholesterol; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium glucose co-transporter-2

Table 2: Clinical outcome from COVID-19 according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
ICU admission, n (%)	108 (14.7)	43 (16.9)	0.442	79 (20.5)	79 (11.6)	<0.001	32 (16.1)	136 (14.3)	0.588	76 (27.8)	17 (2.7)	<0.001
Mechanical ventilation, n (%)	67 (9.1)	24 (9.5)	0.965	51 (13.2)	43 (6.3)	<0.001	22 (11.1)	78 (8.2)	0.244	51 (18.7)	4 (0.6)	<0.001
In-hospital death, n (%)	44 (6.0)	44 (17.3)	<0.001	35 (9.1)	47 (6.9)	0.248	18 (9.1)	71 (7.5)	0.538	32 (11.7)	22 (3.5)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	127 (17.2)	70 (27.6)	0.001	91 (23.6)	109 (16.1)	0.003	40 (20.1)	175 (18.4)	0.642	88 (32.2)	35 (5.6)	<0.001

DPP-4, dipeptidyl peptidase-4; ICU, intensive care unit

Table 3: Multivariate Cox regression for the association between baseline use of glucose lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission	0.53 (0.33, 0.86)	0.01	1.45 (0.96, 2.19)	0.074	0.45 (0.28, 0.74)	0.002	10.95 (5.5, 21.8)	<0.001
Mechanical ventilation	0.51 (0.27, 0.97)	0.041	1.35 (0.78, 2.36)	0.286	0.57 (0.29, 1.11)	0.098	21.99 (4.85, 99.6)	<0.001
In-hospital death	0.51 (0.27, 0.97)	0.039	2.42 (1.25, 4.7)	0.009	0.70 (0.35, 1.39)	0.304	2.86 (1.09, 7.48)	0.033
ICU admission, mechanical ventilation and/or in-hospital death	0.51 (0.34, 0.77)	0.001	1.55 (1.07, 2.24)	0.022	0.46 (0.29, 0.71)	<0.001	6.34 (3.72, 10.78)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), pre-admission use of other glucose-lowering drugs, statins, and RAAS inhibitors, and in-hospital use of other glucose-lowering drugs

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 1: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for comorbidities

Disease	ICD-9-CM Code	Description
Cardiovascular diseases		
Hypertension and hypertensive diseases	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive chronic kidney disease
	404	Hypertensive heart and chronic kidney disease
	405	Secondary hypertension
Coronary heart disease	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	412	Old myocardial infarction
	413	Angina pectoris
	414	Other forms of chronic ischemic heart disease
Heart failure	428	Heart failure
Chronic liver disease		
Chronic liver disease, liver failure, liver cirrhosis and complications	570	Chronic liver disease and cirrhosis
Diabetes mellitus		
Diabetes mellitus	250	Diabetes mellitus
Cancer		
Malignant neoplasm	140-149	Malignant neoplasm of lip, oral cavity, and pharynx
	150-159	Malignant neoplasm of digestive organs and peritoneum
	160-165	Malignant neoplasm of respiratory and intrathoracic organ
	170-176	Malignant neoplasm of bone, connective tissue, skin, and breast
	179-189	Malignant neoplasm of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites
	200-209	Malignant neoplasm of lymphatic and hematopoietic tissue
Cerebrovascular disease		
Cerebrovascular events	430	Subarachnoid haemorrhage
	431	Intracerebral haemorrhage
	432	Other and unspecified intracranial haemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
	438	Late effects of cerebrovascular disease
Chronic obstructive airway disease		
Chronic obstructive pulmonary disease and allied conditions	490-496	Chronic obstructive pulmonary disease and allied conditions
Kidney diseases		
Nephritis, nephrotic syndrome, and nephrosis	581	Nephrotic syndrome
	582	Chronic glomerulonephritis
	583	Nephritis and nephropathy not specified as acute or chronic
	585	Chronic kidney disease
	586	Renal failure, unspecified
	587	Renal sclerosis, unspecified
	588	Disorders resulting from impaired renal function
Others	403.1	Benign hypertensive renal disease
	403.9	Unspecified hypertensive renal disease

04.12404.1	Benign hypertensive heart and renal disease
3	Unspecified hypertensive heart and renal disease
404.1	Polycystic kidney, unspecified type
404.9	Polycystic kidney, autosomal dominant
753.12	Polycystic kidney, autosomal recessive
753.13	Gouty nephropathy
753.14	Postural proteinuria
274.1	Unspecified disorder of kidney and ureter
593.6	
593.9	

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Supplementary Table 2: Baseline clinical characteristics and in-hospital outcome of patients with and without type 2 diabetes admitted with COVID-19 in Hong Kong between January 2020 and February 2021

	Patients with diabetes		Patients without diabetes		
	Number (%) with available data		Number (%) with available data		p-value
Demographics					
Age, years	1220 (100.0)	65.3 (57.1, 73.1)	9839 (100.0)	44.6 (32.3, 58.6)	<0.001
Men, n (%)	1220 (100.0)	662 (54.3)	9839 (100.0)	4047 (47.0)	<0.001
Ex- or current smoker	1220 (100.0)	209 (17.1)	9839 (100.0)	868 (10.1)	0.001
Metabolic parameters					
Diabetes duration, years	1220 (100.0)	1.4 (0.3, 3.4)	-	-	-
BMI, kg/m^2	114 (9.3)	23.6 (21.5, 27.3)	598 (6.1)	23.5 (20.9, 26.5)	0.380
HbA1c, %	886 (72.6)	7.4 (6.6, 9.2)	1901 (19.3)	5.8 (5.4, 6.3)	<0.001
Comorbidities, n (%)					
Hypertension	1220 (100.0)	644 (52.8)	9839 (100.0)	815 (9.5)	<0.001
Coronary heart disease	1220 (100.0)	130 (10.7)	9839 (100.0)	148 (1.7)	<0.001
Heart failure	1220 (100.0)	44 (3.6)	9839 (100.0)	44 (0.5)	<0.001
Cerebrovascular disease	1220 (100.0)	111 (9.1)	9839 (100.0)	148 (1.7)	<0.001
Chronic kidney disease	1220 (100.0)	249 (20.4)	9839 (100.0)	235 (2.7)	<0.001

Chronic liver disease	1220 (100.0)	44 (3.6)	9839 (100.0)	44 (0.5)	<0.001
Chronic obstructive airway disease	1220 (100.0)	61 (5.0)	9839 (100.0)	235 (2.7)	<0.001
Cancer	1220 (100.0)	83 (6.8)	9839 (100.0)	180 (2.1)	<0.001
Baseline drug use, n (%)					
Metformin	1220 (100.0)	737 (60.4)	9839 (100.0)	0	<0.001
Sulphonylureas	1220 (100.0)	385 (31.6)	9839 (100.0)	0	<0.001
DPP-4 inhibitors	1220 (100.0)	199 (16.3)	9839 (100.0)	0	<0.001
Thiazolidinediones	1220 (100.0)	90 (7.4)	9839 (100.0)	0	<0.001
SGLT-2 inhibitors	1220 (100.0)	78 (6.4)	9839 (100.0)	0	<0.001
GLP1 receptor agonists	1220 (100.0)	13 (1.1)	9839 (100.0)	0	0.011
Insulin	1220 (100.0)	273 (22.4)	9839 (100.0)	0	<0.001
Statins	1220 (100.0)	709 (58.1)	9839 (100.0)	572 (6.6)	<0.001
Blood pressure lowering drugs	1220 (100.0)	691 (56.6)	9839 (100.0)	1108 (12.9)	<0.001
RAAS inhibitors	1220 (100.0)	590 (48.4)	9839 (100.0)	452 (5.2)	<0.001
In-hospital treatment, n (%)					
Oseltamivir	1220 (100.0)	16 (1.3)	9839 (100.0)	63 (0.7)	0.051
Ribavirin	1220 (100.0)	396 (32.5)	9839 (100.0)	1823 (21.2)	<0.001
Lopinavir-ritonavir	1220 (100.0)	335 (27.5)	9839 (100.0)	1542 (17.9)	<0.001

Interferon beta	1220 (100.0)	725 (59.4)	9839 (100.0)	2702 (31.3)	<0.001
Antibiotic therapy	1220 (100.0)	755 (61.9)	9839 (100.0)	2769 (32.1)	<0.001
Anti-fungal therapy	1220 (100.0)	124 (10.2)	9839 (100.0)	265 (3.1)	<0.001
Corticosteroid	1220 (100.0)	623 (51.1)	9839 (100.0)	1747 (20.3)	<0.001
Pulse methylprednisolone	1220 (100.0)	5 (0.4)	9839 (100.0)	7 (0.1)	0.011
Intravenous immune globulin	1220 (100.0)	6 (0.5)	9839 (100.0)	9 (0.1)	0.007
Clinical outcome, n (%)					
ICU admission	1220 (100.0)	187 (15.3)	9839 (100.0)	269 (3.1)	<0.001
Mechanical ventilation	1220 (100.0)	110 (9.0)	9839 (100.0)	142 (1.7)	<0.001
In-hospital death	1220 (100.0)	90 (7.4)	9839 (100.0)	105 (1.2)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death	1220 (100.0)	235 (19.3)	9839 (100.0)	340 (3.9)	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HDL, high density-lipoprotein; ICU, intensive care unit; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium glucose co-transporter-2

Supplementary Table 3: Laboratory results on admission and in-hospital treatment of patients with type 2 diabetes according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
Number	737	254		385	679		199	952		273	623	
Laboratory results on admission												
Random glucose, mmol/L	8.1 (6.4, 11.0)	7.1 (6.0, 9.0)	<0.001	8.7 (6.5, 12.1)	7.5 (6.1, 9.7)	<0.001	8.7 (6.6, 11.9)	8.0 (6.4, 11.2)	0.108	9.2 (6.6, 12.8)	7.6 (6.2, 9.5)	<0.001
Sodium, mmol/L	137.0 (134.0, 139.0)	138.0 (135.0, 140.0)	0.018	137.0 (134.0, 139.0)	138.0 (135.0, 140.0)	0.001	136.0 (134.0, 139.0)	137.0 (134.0, 139.0)	0.01	136.0 (133.0, 138.0)	138.0 (136.0, 140.0)	<0.001
Potassium, mmol/L	3.9 (3.6, 4.0)	3.8 (3.5, 4.2)	0.938	3.9 (3.6, 4.3)	3.8 (3.5, 4.2)	<0.001	4.0 (3.7, 4.4)	3.8 (3.5, 4.1)	<0.001	4.0 (3.6, 4.4)	3.8 (3.5, 4.1)	<0.001
Creatinine, µmol/L	77.7 (63.0, 98.0)	83.0 (66.7, 124.0)	<0.001	81.2 (66.0, 110.0)	75.0 (62.8, 95.0)	<0.001	90.0 (70.0, 138.0)	75.0 (62.4, 94.0)	<0.001	91.3 (71.0, 140.0)	72.0 (61.0, 88.1)	<0.001
Albumin, g/L	38.4 (35.0, 41.3)	37.5 (33.0, 41.0)	0.006	38.0 (34.1, 41.0)	38.7 (34.9, 41.7)	0.076	37.0 (33.3, 41.0)	38.7 (35.0, 41.7)	0.019	36.0 (32.0, 39.4)	39.7 (36.0, 42.1)	<0.001
Total bilirubin, µmol/L	7.9 (6.0, 10.2)	8.1 (6.0, 12.0)	0.164	7.8 (6.0, 10.0)	8.0 (5.8, 11.0)	0.580	7.5 (5.4, 10.4)	8.0 (6.0, 11.0)	0.116	8.0 (5.8, 10.6)	8.0 (6.0, 10.6)	0.604
ALP, U/L	67.3 (55.1, 82.0)	74.0 (60.0, 92.4)	<0.001	70.0 (57.0, 84.0)	69.0 (56.0, 84.0)	0.752	70.0 (57.0, 83.0)	69.1 (57.0, 84.8)	0.789	69.3 (55.0, 88.0)	70.0 (57.5, 83.5)	0.843

ALT, U/L	27.0 (18.0, 39.5)	25.1 (16.9, 37.0)	0.295	27.8 (20.0, 39.4)	26.1 (17.0, 41.0)	0.142	26.0 (17.8, 34.9)	27.0 (18.0, 41.7)	0.145	24.4 (17.0, 36.0)	28.6 (19.0, 42.8)	<0.001
LDH, U/L	213.0 (178.0, 277.0)	234.0 (192.0, 303.0)	0.002	214.0 (183.0, 281.0)	219.0 (180.0, 281.0)	0.720	216.0 (190.0, 277.0)	217.0 (181.0, 283.0)	0.505	246.0 (192.0, 362.0)	209.0 (175.0, 254.0)	<0.001
CRP, mg/dL	1.3 (0.4, 4.7)	1.2 (0.3, 5.0)	0.980	1.7 (0.4, 5.4)	1.1 (0.4, 3.9)	0.032	1.5 (0.4, 5.3)	1.3 (0.4, 4.6)	0.376	2.9 (0.5, 7.5)	0.8 (0.3, 2.6)	<0.001
ESR, mm/hour	38.6 (21.0, 65.2)	47.0 (22.5, 84.1)	0.060	43.0 (20.5, 68.0)	37.0 (21.0, 64.0)	0.844	45.6 (21.5, 72.5)	39.8 (21.0, 68.0)	0.622	46.0 (25.0, 80.0)	34.0 (18.5, 53.5)	0.002
Procalcitonin, ng/mL	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.039	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.299	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.308	0.1 (0.1, 0.3)	0.1 (0.1, 0.1)	<0.001
Haemoglobin, g/dL	13.0 (12.0, 14.0)	12.9 (11.6, 14.2)	0.225	12.9 (11.8, 13.9)	13.2 (12.1, 14.3)	0.008	12.9 (11.6, 13.9)	13.2 (12.1, 14.3)	0.003	12.9 (11.5, 14.0)	13.2 (12.1, 14.2)	0.002
White cell count, $x10^9$/L	5.7 (4.6, 7.2)	5.7 (4.4, 7.2)	0.611	5.8 (4.8, 7.4)	5.6 (4.4, 7.0)	0.002	6.1 (4.6, 7.4)	5.6 (4.5, 7.1)	0.031	6.1 (4.8, 8.0)	5.5 (4.4, 6.9)	<0.001
Lymphocyte count, $x10^9$/L	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	0.044	1.2 (0.9, 1.6)	1.2 (0.8, 1.5)	0.451	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	0.138	1.1 (0.8, 1.4)	1.2 (0.9, 1.7)	<0.001
Platelet count, $x10^9$/L	204.0 (160.0, 254.0)	188.0 (149.0, 234.0)	0.003	206.0 (161.0, 258.0)	197.0 (156.0, 243.0)	0.027	204.0 (159.0, 249.0)	198.0 (156.0, 250.0)	0.336	199.0 (151.0, 255.0)	207.0 (166.0, 260.0)	0.101
Prothrombin time, seconds	11.9 (11.3, 12.5)	12.1 (11.4, 12.9)	0.006	11.9 (11.4, 12.6)	11.9 (11.3, 12.5)	0.819	12.1 (11.5, 12.8)	11.9 (11.3, 12.5)	0.026	12.1 (11.5, 12.9)	11.8 (11.2, 12.3)	<0.001
In-hospital treatment, n (%)												

Oseltamivir	9 (1.22)	2 (0.79)	0.739	5.0 (1.3)	10.0 (1.5)	1	3.0 (1.5)	11.0 (1.2)	0.72	7.0 (2.6)	6.0 (1.0)	0.074
Ribavirin	236 (32.0)	84 (33.1)	0.818	125.0 (32.5)	221.0 (32.5)	1	75.0 (37.7)	290.0 (30.5)	0.056	103.0 (37.7)	185.0 (29.7)	0.022
Lopinavir-ritonavir	200 (27.1)	73 (28.7)	0.681	110.0 (28.6)	184.0 (27.1)	0.656	53.0 (26.6)	256.0 (26.9)	1	93.0 (34.1)	125.0 (20.1)	<0.001
Interferon beta	425 (57.7)	164 (64.6)	0.063	220.0 (57.1)	409.0 (60.2)	0.357	122.0 (61.3)	556.0 (58.4)	0.498	187.0 (68.5)	309.0 (49.6)	<0.001
Antibiotic therapy	444 (60.2)	176 (69.3)	0.013	246.0 (63.9)	405.0 (59.6)	0.193	125.0 (62.8)	582.0 (61.1)	0.717	210.0 (76.9)	273.0 (43.8)	<0.001
Anti-fungal therapy	80 (10.9)	26 (10.2)	0.875	52.0 (13.5)	58.0 (8.5)	0.014	32.0 (16.1)	81.0 (8.5)	0.002	47.0 (17.2)	40.0 (6.4)	<0.001
Corticosteroid	367 (49.8)	142 (55.9)	0.108	201.0 (52.2)	330.0 (48.6)	0.286	108.0 (54.3)	475.0 (49.9)	0.296	168.0 (61.5)	203.0 (32.6)	<0.001
Pulse methylprednisolone	2 (0.27)	1 (0.39)	1	1.0 (0.3)	4.0 (0.6)	0.659	0.0 (0.0)	4.0 (0.4)	1	1.0 (0.4)	1.0 (0.2)	0.517
IVIG	2 (0.27)	2 (0.79)	0.272	2.0 (0.5)	2.0 (0.3)	0.623	0.0 (0.0)	5.0 (0.5)	0.594	2.0 (0.7)	0.0 (0.0)	0.093

Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables

ALP, alkaline phosphatase; ALT, alanine transaminase; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; ESR, erythrocyte sedimentation rate; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase

Supplementary Table 4: Incidence rate, per 1,000 person-year, of clinical outcome from COVID-19 according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulfonylureas			DPP4-inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
ICU admission	4176.3	4063.2	0.879	6185.6	3042.6	<0.001	4146.0	3958.9	0.814	7525.9	783.6	<0.001
Mechanical ventilation	2101.5	1885.2	0.648	2894.0	1437.5	0.001	2287.6	1839.8	0.366	3519.7	179.8	<0.001
In-hospital death	1258.8	2946.5	<0.001	1673.1	1454.3	0.530	1561.2	1521.9	0.923	1734.8	977.2	0.036
ICU admission, mechanical ventilation and/or in-hospital death	4914.1	6633.4	0.043	7134.4	4202.9	<0.001	5186.2	5100.3	0.924	8728.4	1615.4	<0.001

DPP-4, dipeptidyl peptidase-4; ICU, intensive care unit

Supplementary Table 5: Multivariate Cox regression with propensity score weighting for the association between baseline use of glucose-lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission, n (%)	0.51 (0.30, 0.86)	0.012	1.42 (0.90, 2.25)	0.131	0.46 (0.28, 0.76)	0.002	9.79 (4.26, 22.50)	<0.001
Mechanical ventilation, n (%)	0.29 (0.12, 0.72)	0.008	1.30 (0.70, 2.44)	0.405	0.42 (0.18, 0.98)	0.044	21.21 (4.40, 102.31)	<0.001
In-hospital death, n (%)	0.45 (0.23, 0.89)	0.022	2.87 (1.40, 5.88)	0.004	0.78 (0.38, 1.59)	0.487	2.86 (0.81, 10.13)	0.103
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	0.53 (0.35, 0.81)	0.003	1.55 (1.02, 2.34)	0.04	0.48 (0.30, 0.76)	0.002	5.90 (3.41, 10.20)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), baseline use of other glucose-lowering drugs, statins and RAAS inhibitors, in-hospital use of other glucose-lowering drugs, and propensity score

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 6: Multivariate Cox regression for the association between baseline use of glucose-lowering drugs and clinical outcome after excluding patients who were identified as having diabetes based on a single fasting plasma glucose (n=25)

	Metformin		Sulfonylureas		DPP4-inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission	0.58 (0.35, 0.97)	0.039	1.48 (0.97, 2.25)	0.067	0.48 (0.29, 0.79)	0.004	12.49 (5.85, 26.68)	<0.001
Mechanical ventilation	0.49 (0.25, 0.97)	0.039	1.36 (0.77, 2.39)	0.286	0.62 (0.32, 1.20)	0.153	34.23 (4.40, 266.34)	<0.001
In-hospital death	0.47 (0.25, 0.90)	0.023	2.36 (1.21, 4.58)	0.011	0.70 (0.35, 1.39)	0.303	3.28 (1.21, 8.91)	0.020
ICU admission, mechanical ventilation and/or in-hospital death	0.53 (0.35, 0.82)	0.004	1.56 (1.07, 2.28)	0.020	0.47 (0.30, 0.74)	<0.001	6.44 (3.71, 11.20)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), baseline use of other glucose-lowering drugs, statins and RAAS inhibitors, and in-hospital use of other glucose-lowering drugs

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10, 25-26
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: a population-wide analysis in Hong Kong

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052310.R2
Article Type:	Original research
Date Submitted by the Author:	03-Oct-2021
Complete List of Authors:	Luk, Andrea; The Chinese University of Hong Kong Faculty of Medicine, Medicine and Therapeutics Yip, Terry C.F.; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Zhang, Xinge; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Kong, Alice Pik Shan; The Chinese University of Hong Kong, Prince of Wales Hosopital Wong, Vincent Wai-Sun; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Ma, Ronald; Chinese University of Hong Kong, Medicine and Therapeutics, Prince of Wales Hospital; Chinese University of Hong Kong, Hong Kong Institute of Diabetes and Obesity Wong, Grace ; The Chinese University of Hong Kong, Department of Medicine and Therapeutics
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Infectious diseases
Keywords:	COVID-19, DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: a population-wide analysis in Hong Kong

Running title

Glucose-lowering drugs and COVID-19

Authors

Andrea O.Y Luk[1,2]

Terry C.F. Yip[3]

Xinge Zhang[1]

Alice P.S Kong[1,2]

Vincent W.S Wong[3]

Ronald C.W Ma[1,2]

Grace L.H Wong[3]

*AOY Luk and YCF Yip contributed equally

Affiliation

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [2]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [3]Department of Medicine and Therapeutics, Medical Data Analytics Centre, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

Corresponding author

Grace L.H. Wong

Department of Medicine and Therapeutics

The Chinese University of Hong Kong

9/F Lui Che Woo Clinical Sciences Building

Prince of Wales Hospital

30-32 Ngan Shing Street

Shatin, New Territories

Hong Kong Special Administrative Region

People's Republic of China

Tel: 852-3505-3528

email: wonglaihung@cuhk.edu.hk

Word count: 3,489

Number of table: 3

Abstract

Objectives: To investigate the association between baseline use of glucose-lowering drugs and serious clinical outcome among patients with type 2 diabetes.

Design: Territory-wide retrospective cohort of confirmed cases of COVID-19 between January 2020 and February 2021.

Setting: All public health facilities in Hong Kong.

Participants: 1,220 patients with diabetes who were admitted for confirmed COVID-19.

Primary and secondary outcome measures: Composite clinical endpoint of intensive care unit (ICU) admission, requirement of invasive mechanical ventilation, and/or in-hospital death.

Results: In this cohort (median age 64.7 years, 54.3% men), 737 (60.4%) patients were treated with metformin, 385 (31.6%) with sulphonylureas, 199 (16.3%) with DPP-4 inhibitors, and 273 (22.4%) with insulin prior to admission. In multivariate Cox regression, use of metformin and DPP-4 inhibitors was associated with reduced incidence of the composite endpoint relative to non-use, with respective hazard ratios (HRs) of 0.51 (95% confidence interval [CI] 0.34, 0.77, p=0.001) and 0.46 (95% CI 0.29, 0.71, p<0.001), adjusted for age, sex, diabetes duration, HbA1c, smoking, comorbidities and drugs. Use of sulphonlyureas (HR 1.55, 95% CI 1.07, 2.24, p=0.022) and insulin (HR 6.34, 95% CI 3.72, 10.78, p<0.001) were both associated with increased hazards of the composite endpoint.

Conclusions: Users of metformin and DPP-4 inhibitors had fewer adverse outcomes from COVID-19 compared with non-users, whereas insulin and sulphonylurea might predict a worse prognosis.

Strengths and limitations of this study

- This cohort study included over 95% of all patients with COVID-19 in Hong Kong in the study period.
- Statistical methods including multivariable adjustment and propensity score weighting have been adopted to adjust for important confounders of the clinical endpoints.
- The study is an observational retrospective cohort study with inherent limitations related to unmeasured confounding.
- The study is not able to infer causality given the likelihood of confounding by indication, e.g. with respect to metformin and insulin use.
- We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

Introduction

Patients with diabetes are more likely to have serious outcomes from coronavirus infections including severe acute respiratory syndrome (SARS), Middle-East respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19) (1-6). In a population-based analysis of in-hospital fatalities due to COVID-19 in the United Kingdom, type 1 diabetes and type 2 diabetes were associated with increased odds of 3.5 and 2.0 for death, adjusted for age, sex and sociodemographic factors (6). The excess deaths might be related to co-occurrence of other medical conditions such as obesity and cardiovascular diseases that are independent risk factors for adverse outcomes (7-10). Furthermore, diabetes gives rise to aberrant inflammatory responses which predispose to more intense lung infiltration, cytokine storm and multiorgan failure (11). Pro-inflammatory indicators such as interleukin (IL)-6, IL-2 receptor, procalcitonin, tumour necrosis factor (TNF)-α and C-reactive protein (CRP) levels are generally higher in patients with diabetes compared with those without diabetes (12).

Several glucose-lowering drug classes have immunomodulatory effects. Metformin activates AMP-activated protein kinase (AMPK) which in turn suppresses a number of inflammatory pathways including nuclear factor kappa B and mammalian target of rapamycin (13,14).

Activation of AMPK also stabilises angiotensin converting enzyme (ACE) 2, the vasodilator effect of which improve organ blood flow and may protect against lung injury (15). Both observational cohort and randomised controlled studies reported reduced risks of pneumonia and other infections with metformin therapy (16,17). Dipeptidyl peptidase-4 (DPP-4), also known as cluster of differentiation (CD) 26, is expressed in immune cells and is implicated in the regulation of adaptive immunity (18). In a case-control study of patients with COVID-19, in-hospital treatment with sitagliptin was linked to improved survival and other measures of clinical outcome (19). However, the beneficial effects of DPP-4 inhibitors have not been supported by other studies (20-22). In a territory-wide retrospective cohort of confirmed cases of COVID-19 between January 2020 and February 2021, we investigated the association between baseline use of glucose-lowering drugs and serious clinical outcomes among patients with type 2 diabetes.

Methods

Setting and patients

The Hong Kong Hospital Authority (HA) governs all public hospitals and general out-patient departments in the territory and provides care for approximately 80% of local residents (23). Given the high cost differential in healthcare between the public and private sector with the private sector being significantly more expensive, people who utilise health services in the private sector are usually at a more favourable socioeconomic position. Since the beginning of the pandemic, all cases of COVID-19, including symptomatic cases presented to out-patient clinics or hospitals, asymptomatic contacts of confirmed cases, and inbound travellers, were admitted to HA healthcare facilities. Clinical data including past medical diagnoses, drug prescription records, laboratory results, admission records and vital status were captured in the

Clinical Data Analysis and Reporting System (CDARS), an electronic medical record system used in the Hong Kong HA. We retrieved data of all patients presented with COVID-19 who admitted between 23 January 2020 (the first case in Hong Kong) and 28 February 2021 (24). All patient data were anonymised to ensure confidentiality. Patients aged below 18 years were excluded. This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Data collection

Patients with COVID-19 were identified based on positive SARS-CoV-2 polymerase chain reaction in nasopharyngeal swab in any one of the HA laboratories (25). For each patient, we obtained demographic data (age, sex), relevant diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, drug prescription record for at least 12 months before admission, laboratory results for plasma glucose, HbA1c and lipid profile for at least 12 months before admission, as well as plasma glucose, kidney function, liver function, inflammatory markers, haematology and coagulation study on the day of admission. Progress during admission including treatment with corticosteroid, intravenous immunoglobulin, anti-viral therapy, anti-fungal therapy, antibiotic therapy, mechanical ventilation, and transfer to intensive care unit (ICU) were also retrieved. Patients were followed from the date of diagnosing COVID-19 until discharge from hospital or death. Data capture was censored on 24 April 2021.

Definition and outcome

A patient was classified to have type 2 diabetes if he or she fulfilled one or more of the following criteria within 12 months before admission: use of non-insulin glucose-lowering drugs for at

least one day, continuous use of insulin for ≥28 days, HbA1c ≥6.5% in any one measurement, fasting plasma glucose ≥7.0 mmol/L in any one measurement, and/or diagnosis code of type 2 diabetes based on ICD-9-CM.

Baseline use of glucose-lowering drugs, including metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), and insulin, was identified based on prescription record of the respective drug. Patients were considered to be baseline users if a prescription record was found within 12 months before and up to the day of admission. Patients were considered to be non-users if a prescription record was not found within 12 months before admission, on the day of and during admission. We have not set a minimum exposure time to define users because patients who attended the private sector for diabetes treatment would not have any prescription records in the HA CDARS before admission, but they would have a prescription record on the day of admission indicating their pre-admission use of the drug. The proportion of patients receiving medical care in the private sector is around 10% (23).

Relevant comorbidities were identified as follows: hypertension was defined as the use of blood pressuring lowering drugs within 12 months before admission and/or ICD-9-CM code of hypertension (Supplementary Table 1); chronic kidney disease was defined as having an estimated glomerular filtration rate <60 ml/min/1.73m^2 as determined using the Chronic Kidney Disease Epidemiology Collaboration equation within 12 months prior to admission and/or ICD-9-CM codes of kidney diseases (Supplementary Table 1); chronic liver disease, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive airway disease and

cancer were defined based on ICD-9-CM codes (Supplementary Table 1). The use of ICD-9-CM codes in CDARS to identify medical conditions has been shown to be 99% accurate when referenced to clinical, laboratory, imaging and endoscopy results from the electronic medical records (26). Clinical endpoints included ICU admission, mechanical ventilation, in-hospital death, and composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death. For the composite endpoint, patients were followed from the date of diagnosing COVID-19 until the date of ICU admission, use of mechanical ventilation, in-hospital death, or discharge from hospital, whichever came first. For the individual clinical endpoint, patients were followed from the date of diagnosing COVID-19 until the date of the occurrence of that individual clinical endpoint or discharge from hospital, whichever came first.

Statistical analysis

Analysis was conducted using R software (4.0.0). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and categorical variables as number (percentages). Between-group comparison was conducted by chi-square test for categorical variables, Student's t-test for normally distributed continuous variables, and Kruskal-Wallis test for continuous variables with skewed distribution. Clinical characteristics were compared between users and non-users of metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), and insulin. Due to small number, use of thiazolidinediones, glucagon-like peptide-1 receptor agonists and sodium-glucose transport protein 2 inhibitors were not tested. Multivariate Cox regression was conducted to derive the hazard ratios (HRs) and 95% confidence intervals (CIs) of use versus non-use of metformin, sulphonylureas, DPP-4 inhibitors

and insulin for primary and secondary clinical endpoints. The multivariate Cox model was adjusted for age, sex, diabetes duration, smoking, HbA1c, comorbidities (history of hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, and cancer), baseline use of other glucose-lowering drugs, statins and renin-angiotensin-aldosterone system (RAAS) inhibitors, and in-hospital use of other glucose-lowering drugs. The multivariate Cox regression was limited to patients with available HbA1c measurement (n=886) in whom the latest HbA1c obtained within 12 months of hospital admission was used. The selection of variables was based on known or possible link between these variables and clinical endpoints. Due to the small proportion of patients with available data on body mass index (BMI) (9.3%), BMI was not included in the multivariate Cox regression model. In a sensitivity analysis, we generated propensity scores for glucose-lowering drug use using logistic regression model that contained age, sex, smoking, diabetes duration, comorbidities and baseline use of other glucose lowering drugs, statins and RAAS inhibitors using the overlap propensity score weighting method (27). The weights were included in the multivariate Cox models to balance the differences in patient characteristics between glucose-lowering drug use groups. We also repeated the multivariate Cox regression excluding patients whose diabetes status was established by a single fasting plasma glucose measurement only, as these patients might not have diabetes.

Patient and Public Involvement

There was no patient of public involvement.

Results

Baseline clinical characteristics by glucose lowering drug classes

Of 9,839 adult patients with COVID-19, 1,220 patients (12.4%) had type 2 diabetes. Patients with diabetes were older, had a male preponderance and higher frequencies of comorbidities than those without diabetes (Supplementary Table 2). In patients with diabetes, 737 (60.4%) were treated with metformin, 385 (31.6%) with sulphonylureas, 199 (16.3%) with DPP-4 inhibitors, and 273 (22.4%) with insulin at baseline. Generally, users of each of the glucose-lowering drug class had longer diabetes duration and higher HbA1c levels than non-users of the respective drug class, whereas BMI did not differ (Table 1). Metformin users were younger and users of insulin and DPP-4 inhibitors were older than their respective non-users, whilst no age difference was detected between users and non-users of sulphonylureas (Table 1). Coronary heart disease and heart failure were less common in metformin users and more common in insulin users when compared to their respective non-users (Table 1). Chronic kidney disease was also less common in metformin users but more prevalent among users than non-users of other glucose-lowering drug classes (Table 1).

Markers of disease severity and outcome by glucose lowering drug classes

On admission, random plasma glucose levels were higher in users than non-users of most oral glucose-lowering drugs, except for DPP-4 inhibitors (Supplementary Table 3). In addition, metformin users had higher lymphocyte count, lower alkaline phosphatase (ALP) levels and lactate dehydrogenase (LDH) levels than metformin non-users (Supplementary Table 3). Users of sulphonylureas had higher CRP levels and total white cell count, and users of DPP-4 inhibitors had higher total white cell count compared with respective non-users (Supplementary Table 3). Insulin users had higher plasma glucose levels, higher levels of most inflammatory

markers including LDH, CRP, erythrocyte sedimentation rate and procalcitonin, and lower lymphocyte count than insulin non-users (Supplementary Table 3).

There were overall no differences in the proportion of patients receiving most types of anti-microbial therapy, corticosteroid and IVIG between users and non-users of metformin, sulphonylureas and DPP-4 inhibitors, with the exception of less frequent administration of antibiotics among metformin users and more frequent use of anti-fungal therapy among users of sulphonylureas and DPP-4 inhibitors (Supplementary Table 3). Insulin users were more likely to be treated with anti-microbial therapy and corticosteroid than non-users (Supplementary Table 3).

During admission, 235 patients (19.3%) developed composite primary endpoint, 187 patients (15.3%) were transferred to ICU, 110 patients (9.0%) required mechanical ventilation, and 90 patients (7.4%) died. Fewer metformin users reached composite endpoint (Proportions: 17.2% versus 27.6%, p=0.001; Incidence rates: 4914.1 versus 6633.4 per 1,000 person-year, p=0.043) or died (Proportions: 4.0% versus 17.3%, p<0.001; Incidence rates: 1258.8 versus 2946.5 per 1,000 person-year, p<0.001) compared with non-users (Table 2, Supplementary Table 4). Users of sulphonlyureas and insulin were more likely than non-users to reach composite endpoint, required ICU admission and mechanical ventilation, and insulin users were also more likely to die than non-users (Table 2, Supplementary Table 4). The proportion of patients developing primary or secondary endpoints were similar between users and non-users of DPP-4 inhibitors (Table 2, Supplementary Table 4).

Association between pre-admission use of glucose lowering drugs and clinical outcome

In multivariate Cox regression model, baseline use of metformin was associated with reduced hazards of composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death (adjusted HR 0.51 [95% CI 0.34, 0.77], p=0.001) and individual endpoints of ICU admission (adjusted HR 0.53 [95% CI 0.33, 0.86], p=0.010), mechanical ventilation (adjusted HR 0.51 [95% CI 0.27, 0.97], p=0.041) and in-hospital death (adjusted HR 0.51 [95% CI 0.27, 0.97], p=0.039) relative to non-use (Table 3). Baseline use of DPP-4 inhibitors was associated with reduced hazards of composite endpoint (adjusted HR 0.46 [95% CI 0.29, 0.71], p<0.001) and ICU admission (adjusted HR 0.45 [95% CI 0.28, 0.74]. p=0.002) (Table 3). Use of sulphonlyureas (adjusted HR 1.55 [95% CI 1.07, 2.24], p=0.022) and insulin (adjusted HR 6.34 [95% CI 3.72, 10.78], p<0.001) were both associated with increased hazards of the composite endpoint (Table 3). Sensitivity analysis using multivariate Cox regression with propensity score weighting yielded similar findings (Supplementary Table 5). Exclusion of patients who were identified as having diabetes based on a single fasting plasma glucose measurement (n=25) had minimal effect on the results (Supplementary Table 6).

Discussion

In a territory-wide cohort of patients with diabetes presented with COVID-19, we showed that pre-admission use of metformin and DPP-4 inhibitors was linked to reduced risks of serious outcome, whereas the use of sulphonylureas and insulin was associated with a worse prognosis Our findings corroborate and extend the results of previous studies and suggest a possible protective role of metformin and DPP-4 inhibitors against severe respiratory tract infection. The strength of our study includes the unbiased nature of the cohort as the database captured all

patients with COVID-19 in Hong Kong. Both symptomatic and asymptomatic patients were admitted to healthcare facilities and their clinical data were included in the present analysis. Furthermore, the use of a universal electronic medical record for drug prescription ensures that we have accurately classified use and non-use of different glucose-lowering drug classes.

Metformin, infection and COVID-19

Several observational studies in patients hospitalised with COVID-19 reported the association between metformin use and death and other measures of adverse outcome (22, 28-31). In a nationwide study conducted in England including 2.85 million patients with type 2 diabetes among whom 13,479 had a record of COVID-19-related deaths, those prescribed metformin had fewer deaths with adjusted HR 0.77 when compared to those not prescribed metformin (22). In another study of 6,256 patients (mean age 75 years) with either type 2 diabetes or obesity admitted with COVID-19 in the United States (U.S), metformin use was found to reduce the risk of death in women with HR 0.79 adjusted for age and comorbidities although no effect was observed in men (28). Two meta-analyses also noted a protective effect of metformin with pooled odds ratios of around 0.6 for mortality from COVID-19 (32,33). However, in an analysis of 1,317 patients (mean age 70 years) with COVID-19 and diabetes in France, metformin was associated with fewer deaths in univariate but not in multivariate analysis (7). Similarly, among 1,297 patients (mean age 75 years) with diabetes hospitalised for COVID-19 in Spain, the group on metformin were less likely to die and/or require ICU admission or mechanical ventilation than non-users, but no difference was detected when the two groups were propensity matched for demographics, comorbidities and drugs (20). In the present study, we found that metformin was associated with 50% reduction in the risk of in-hospital deaths and 50% reduction in the risk of

composite clinical endpoint. The inconsistency in findings between studies could be due to a number of factors, including but not limited to differences in age and disease characteristics of the patient cohorts and in the statistical methods used to examine drug effects. One of the limitations of our study is the high proportion of patients with missing information on anthropometric measures and we did not include these variables in multivariate adjustment. Previous studies have reported a U-shape relationship between BMI and deaths from COVID-19 in people with and without diabetes (34, 35). Obesity alters the mechanics of the lungs and chest wall which increases the susceptibility to respiratory failure during infection. Furthermore, confounding by indication remained an important source of bias in our study as patients who were not prescribed metformin might have other medical conditions, for example, malnutrition, kidney or liver diseases, that contraindicated the use of metformin and conferred a poorer prognosis from COVID-19 (36). Nonetheless, our results are in line with most other studies suggesting possible benefits of metformin, or at least no evidence of harm, in patients with type 2 diabetes afflicted by COVID-19.

The immunomodulatory action of metformin has been demonstrated in cell and animal models as well as in human studies, and is independent of the metabolic function of the drug (13). In a recent randomised control trial of 53 patients taking systemic glucocorticoid for inflammatory diseases, those assigned metformin had reduced levels of high sensitivity CRP and neutrophil counts, accompanied by lower frequencies of pneumonia and moderate-to-severe infection than the placebo arm over a 12-week period (37). In the present study, metformin users had lower LDH levels and higher lymphocyte counts on admission than non-users. In infected patients,

metformin may dampen the exaggerated immune reaction to SARS-CoV-2 which is causal for the development of severe lung injury and cytokine storms associated with type 2 diabetes (11).

DPP-4 inhibitors and COVID-19

Dipeptidyl-peptidase-4 inhibitors have pleiotropic effects on the immune system and the effect of this drug class as an ancillary treatment of inflammatory diseases such as rheumatoid arthritis and viral infections have been previously examined (18). Moreover, DPP-4 is a known receptor for MERS-CoV in human. It has been speculated that DPP-4 may also mediate the entry of SARS-CoV-2, although the evidences for this are yet to be consolidated (38,39). In an Italian study of 338 patients with diabetes admitted with COVID-19, in-hospital initiation of sitagliptin reduced deaths by 56% and ICU admission by 49% (19). Another case series in Italy including 90 patients with diabetes reported fewer COVID-19-related deaths among prevalent users of DPP-4 inhibitors adjusted for age and sex (40). In the present study, baseline use of DPP-4 inhibitors was associated with reduced risk of composite clinical endpoint although in-hospital deaths were not reduced. Notably, several observational studies and a meta-analysis did not find an association between DPP-4 inhibitors and complications from COVID-19 (20,21,41). In particular, in the large study conducted in England, COVID-19-related deaths occurred more frequently in patients prescribed DPP-4 inhibitors (22). Differences in statistical procedures may account for the inconsistent findings. Further studies are needed to investigate whether long-term exposure of this drug class can improve prognosis of coronavirus infection.

Insulin and COVID-19

We revealed a positive relationship between pre-admission insulin use and composite clinical outcome, driven mainly by increased hazards for ICU admission and mechanical ventilation among insulin users. Our results are consistent with several other studies suggesting that insulin use may predict a worse outcome from COVID-19 (20,42). Insulin therapy is usually initiated late in the diabetes continuum and it is very possible that the positive association between insulin use and adverse outcome was due to incomplete statistical removal of confounding by indication. In the present study, insulin users were significantly older and were more likely to have premorbid kidney and cardiovascular diseases. On admission, insulin users also had higher inflammatory markers and lower lymphocyte counts which are important severity indicators. Although insulin therapy is deemed the most appropriate glucose-lowering option during acute illnesses, high level of vigilance should be maintained in managing patients on chronic insulin therapy who have a greater likelihood of deterioration.

Sulphonylurea and COVID-19

The risk association between sulphonylureas and in-hospital death was less expected and not well explained. In Hong Kong, sulphonylureas is widely prescribed as a second-line drug after metformin. In the present cohort, the frequencies of comorbidities were mostly balanced between users and non-users of sulphonylureas with the exception of a higher prevalence of chronic kidney disease among users. Previous studies on COVID-19 did not show harm associated with sulphonylurea use. Glyburide has been shown to suppress the immune system but studies on the use of sulphonylurea with infection outcome have produced mixed results (43).

Limitations

We acknowledge the following limitations. This was an observational cohort study with inherent limitations related to unmeasured confounding. Metabolic parameters including BMI were not available in a large proportion of patients and these variables were not included in the statistical adjustment. Among people with available BMI data, the mean BMI did not differ between users and non-users of glucose-lowering drug classes. Hence, we would speculate that the lack of adjustment for BMI in the Cox regression would not have made significant impact on the results. Despite statistical efforts to adjust for comorbidities, we could not fully address residual confounding by drug indication. In this connection, our results cannot be taken to infer causality between drug use and clinical outcome. Although we have included over 95% of all patients with COVID-19 in Hong Kong, the size of our cohort was relatively small. We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

Conclusion

In this retrospective cohort of Chinese with type 2 diabetes, background use of metformin and DPP-4 inhibitors was associated with fewer complications of COVID-19, whereas insulin and sulphonylureas predicted a worse prognosis. Given the increased risk for serious infection in patients with diabetes, drugs with off-target action in immune pathways could be further evaluated for potential new application beyond the ambit of their original indication and assessed for use in modifying outcome from infectious diseases.

Funding

This study has received no financial support.

Author contributions

A.O.Y.L. and T.C.F.Y. contributed to conception of the article, results interpretation, drafted the manuscript and approved the final version. G.L.H.W. contributed to conception of the article, data acquisition and approved the final version. X.Z. contributed to conception of the article, statistical analysis and approved the final version. A.P.S.L., V.W.S.W. and R.C.W.M. contributed to conception of the article and approved the final version. G.L.H.W. is the guarantor of this work, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

Andrea Luk has served as a member of advisory panel for Amgen, AstraZeneca, Boehringer Ingelheim and Sanofi and received research support from Amgen, Asia Diabetes Foundation, Bayer, Boehringer Ingelheim, Lee's Pharmaceutical, MSD, Novo Nordisk, Roche, Sanofi, Sugardown Ltd, Takeda.

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences.

Xinge Zhang has no competing interests to report.

Alice Kong has received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Merck Serono, Nestle, Novo Nordisk, Pfizer and Sanofi.

Vincent Wong has served as an advisory committee member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH and Terns; and a speaker for Bristol-Myers

Squibb, Echosens, Gilead Sciences and Merck. He has also received a research grant from Gilead Sciences.

Ronald Ma has received research funding from AstraZeneca, Bayer, Merck Sharp & Dohme, Novo Nordisk, Pfizer and Tricida Inc. for carrying out clinical trials, and has received speaker honorarium or consultancy in advisory boards from AstraZeneca, Bayer and Boehringer Ingelheim. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research.

Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen, as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen and Roche, and received research grant from Gilead Sciences.

Data availability statement

No additional data are available.

Ethics Statement

This study involves human participants and was approved by an Ethics Committee(s) or Institutional Board(s): The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (the Joint CUHK-NTEC CREC), reference number: 2021.239.

References

1. Assiri A, AI-Tawfiq JA, AI-Rabeeah AA, AI-Rabiah FA, AI-Hajjar S, AI-Barrak A, Flemban H, AI-Nassir WN, Balkhy HH, AI-Hakeem RF, Makhdoom HQ, Zumla AI, Memish ZA. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013;13:752-761
2. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623-628
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720
4. Wu J, Zhang J, Sun X, Wang L, Xu Y, Zhang Y, Liu X, Dong C. Influence of diabetes melllitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. Diabetes Obes Metab 2020;22:1907-1914
5. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M; COVID-19

Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-1355

6. Emma B, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a while-population study. Lancet Diabetes Endocrinol 2020;8:813-822
7. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébaut JF, Thivolet C, Tramunt B, Vatier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500-1515
8. Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and Coronavirus Disease 2019. Diabetes Care 2020;43:2339-2344
9. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, Hegde AA, Drazner MH, Neeland IJ, Grodin JL. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: Results from the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation 2021;143:135-144

10. Cummings MJ, Baldwin MR, Abrams D, Jocobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, Hochman BR, Salazar-Schicchi J, Yip NH, Brodie D, O'Donnell MR. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763-1770

11. Mauvais-Jarvis F. Aging, male sex, obesity and metabolic inflammation create the perfect storm for COVID-19. Diabetes 2020;69:1857-1863

12. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diab Res Care 2020;8:e001343

13. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab 2014; 20:953-966

14. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, McNeilly AD, Balfour DJ, Savinko T, Wong AK, Viollet B, Sakamoto K, Fagerholm SC, Foretz M, Lang CC, Rena G. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119:652-665

15. Zhang J, Dong J, Martin M, He M, Gongol B, Marin TL, Chen L, Shi X, Yin Y, Shang F, Wu Y. AMP-activated protein kinase phosphorylation of angiotensin-converting enzyme 2 in endothelium mitigates pulmonary hypertension. Am J Respir Crit Care Med 2018;198:509-520

16. Liang H, Ding X, Li L, Wang T, Kan Q, Wang L, Sun T. Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Crit Care 2019;23:50

17. Zhang M, He JQ. Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis. Eur J Clin Pharmacol 2020;76:149-159

18. Shao S, Xu QQ, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacol Ther 2020;209:107503

19. Solerte SB, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, Dell'Acqua M, Ippolito E, Scaranna C, Bellante R, Galliani S, Dodesini AR, Lepore G, Geni F, Fiorina RM, Catena E, Corsico A, Colombo R, Mirani M, De Riva C, Oleandri SE, Abdi R, Bonventre JV, Rusconi S, Folli F, Di Sabatino A, Zuccotti G, Galli M, Fiorina P. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: A multicenter, case-control, retrospective, observational study. Diabetes Care 2020;43:2999-3006

20. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD, Ayala-Gutiérrez MM, Fuentes-Jiménez F, Huerta LJ, Muñoz JA, Rubio-Rivas M, Madrazo M, Garcia MG, Montes BV, Sola JF, Ena J, Ferrer RG, Pérez CM, Ripper CJ, Lecumberri JJN, Acedo IEA, Canteli SP, Cosío SF, Martínez FA, Rodríguez BC, Pérez-Martínez P, Ramos-Rincón JM, Gómez-Huelgas R; SEMI-COVID-19 Network. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Med 2020;18:359

21. Fadini GP, Morieri ML, Longato E, Bonora BM, Pinelli S, Selmin E, Voltan G, Falaguasta D, Tresso S, Costantini G, Sparacino G, Di Camillo B, Tramontan L, Cattelan AM, Vianello A, Fioretto P, Vettor R, Avogaro A. Exposure to dipeptidyl-peptidase-4

inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab 2020;22:1946-1950

22. Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, Kar P, Meace C, Sattar N, Sharp S, Wareham NJ, Weaver A, Woch E, Young B, Valabhji J. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol 2021; 9:293-303
23. Census and Statistic Department. Thematic Household Survey Report No. 50. Hong Kong SAR: Census and Statistics Department, 2013. https://www.statistics.gov.hk/pub/B11302502013XXXXB0100.pdf (Accessed date: 3 February 2021)
24. Yip TC, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut 2020 [Online ahead of print]
25. Lui GC, Yip TC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Chan HL, Hui DS, Wong GL. Significantly Lower Case-fatality Ratio of Coronavirus Disease 2019 (COVID-19) than Severe Acute Respiratory Syndrome (SARS) in Hong Kong-A Territory-Wide Cohort Study. Clin Infect Dis 2020 [Online ahead of print]
26. Wong JC, Chan HL, Tse YK, Yip TC, Wong VW, Wong GL. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. Aliment Pharmacol Ther 2017;46:1001-1010
27. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol 2019;188:250-257

28. Bramante C, Ingraham N, Murray T, Marmor S, Hoversten S, Gronski J, McNeil C, Feng R, Guzman G, Abdelwahab N, King S, Meehan T, Benson B, Pendleton K, Vojta D, Tignanelli CJ. Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. medRxiv 2020;2020.06.19.20135095

29. Lally MA, Tsoukas P, Halladay CW, O'Neill E, Gravenstein S, Rudolph JL. Metformin is associated with decreased 30-day mortality among nursing home residents infected with SARS-CoV2. J Am Med Dir Assoc 2021; 22:193-198

30. Crouse A, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. medRxiv 2020;2020.07.29.20164020

31. Do JY, Kim SW, Park JW, Cho KH, Kang SH. Is there an association between metformin use and clinical outcomes in diabetes patients with COVID-19? Diabetes Metab 2020;S1262-3636(20)30159-2 [Online ahead of print]

32. Henrina J, Lim MA, Lawrensia S, Suastika K. The effect of metformin consumption on mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab Syndr 2020; 14:2177-2183

33. Kow CS, Hasan SS. Mortality risk with preadmission metformin use in patients with COVID-19 and diabetes: A meta-analysis. J Med Virol 2021; 93:695-697

34. Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, Jebb SA. Associations between body-mass index and COVID-19 severity in 6.9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol 2021; 9:350-359

35. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol 2020; 8:823-833

36. Wong GL, Wong VW, Thompson A, Jia J, Hou J, Lesmana CRA, Susilo A, Tanaka Y, Chan WK, Gane E, Ong-Go AK, Lim SG, Ahn SH, Yu ML, Piratvisuth T, Chan HL; Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. Lancet Gastroenterol Hepatol 2020;5:776-787

37. Pernicova I, Kelly S, Ajodha S, Sahdev A, Bestwick JP, Gabrovska P, Akanle O, Ajjan R, Kola B, Stadler M, Fraser W, Christ-Crain M, Grossman AB, Pitzalis C, Korbonits M. Metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. Lancet Diabetes Endocrinol 2020;8:278-291

38. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251-254

39. Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes Metab Res Rev 2020; 36:e3330

40. Mirani M, Favacchio G. Carrone F, Betella N, Biamonte E. Morenghi E, Mazziotti G, Lania AG. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4

inhibitors in patients with type 2 diabetes with COVID-19: A case series from an academic hospital in Lombardy, Italy. Diabetes Care 2020;43:3042-3049

41. Hariyanto TI, Kurniawan A. Dipeptidyl peptidase 4 (DPP4) inhibitor and outcome from coronavirus disease 2019 (COVID-19) in diabetic patients: a systematic review, meta-analysis, and meta-regression. J Diabetes Metab Disord 2021; 20:1-8
42. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiang M, Deng A, Zhang Y, Zheng L, Huang K. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care 2020;43:1399-1407
43. Koh GC, Maude RR, Schreiber MF, Limmathurotsakul D, Wiersinga WJ, Wuthiekanun V, Lee SJ, Mahavanakul W, Chaowagul W, Chierakul W, White NJ, van der Poll T, Day NP, Dougan G, Peacock SJ. Glyburide is anti-inflammatory and associated with reduced mortality in melioidosis. Clin INfect Dis 2011;52:717-725

Table 1: Clinical characteristics of patients with type 2 diabetes according to pre-admission use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin.

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	*P*	Users	Non-users	*P*	Users	Non-users	*P*	Users	Non-users	*P*
Number	737	254		385	679		199	952		385	679	
Demographics												
Age, years	65.6 (57.7, 72.6)	68.9 (61.3, 79.7)	<0.001	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656	67.0 (58.4, 75.5)	65.1 (56.8, 72.2)	0.029	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656
Men, n (%)	405 (55.0)	131 (51.6)	0.391	222 (57.7)	350 (51.5)	0.063	118 (59.3)	506 (53.2)	0.133	222 (57.7)	350 (51.5)	0.063
Ex-/active smoker, n (%)	125 (17.0)	49 (19.3)	0.443	70 (18.2)	113 (16.6)	0.687	34 (17.1)	163 (17.1)	0.818	70 (18.2)	113 (16.6)	0.687
Metabolic parameters												
Diabetes duration, years	1.8 (1.4, 6.4)	1.2 (0.5, 2.5)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001	3.9 (1.5, 11.3)	1.4 (0.0, 1.9)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001
BMI, kg/m^2	24.1 (21.5, 27.7)	23.7 (22.2, 27.0)	0.670	24.4 (21.8, 27.8)	23.5 (21.5, 27.0)	0.382	25.0 (18.7, 27.0)	23.3 (21.6, 27.4)	0.636	22.9 (19.8, 25.9)	24.4 (22.2, 27.4)	0.051
HbA1c, %	7.3 (6.6, 8.5)	6.6 (6.1, 7.8)	<0.001	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001	7.6 (6.8, 8.9)	7.2 (6.5, 8.9)	0.027	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001
LDL-C, mmol/L	2.1 (1.7, 2.7)	2.4 (1.7, 3.0)	0.004	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081	2.0 (1.5, 2.5)	2.3 (1.7, 2.8)	<0.001	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081
HDL-C, mmol/L	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	0.857	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.311	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17
Triglyceride, mmol/L	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)	0.093	1.3 (1.0, 1.9)	1.36 (0.9, 2.0)	0.666	1.4 (1.0, 1.9)	1.4 (1.0, 2.0)	0.774	1.3 (1.0, 1.9)	1.36 (0.9, 2.0)	0.666
Comorbidities, n (%)												
Hypertension	465 (63.1)	144 (56.7)	0.083	267 (69.4)	329 (48.5)	<0.001	123 (61.8)	498 (52.3)	0.018	267 (69.4)	329 (48.5)	<0.001
Coronary heart disease	76 (10.3)	48 (18.9)	0.001	45 (11.7)	79 (11.6)	1	30 (15.1)	96 (10.1)	0.054	45 (11.7)	79 (11.6)	1
Heart failure	22 (3.0)	22 (8.7)	<0.001	13 (3.4)	29 (4.3)	0.578	11 (5.5)	32 (3.4)	0.208	13 (3.4)	29 (4.3)	0.578
Cerebrovascular disease	66 (9.0)	40 (15.7)	0.004	31 (8.1)	72 (10.6)	0.213	26 (13.1)	82 (8.6)	0.068	31 (8.1)	72 (10.6)	0.213
Chronic kidney disease	144 (19.5)	96 (37.8)	<0.001	98 (25.5)	135 (19.9)	0.042	72 (36.2)	164 (17.2)	<0.001	98 (25.5)	135 (19.9)	0.042
Chronic liver disease	26 (3.5)	17 (6.7)	0.05	16 (4.2)	27 (4.0)	1	9 (4.5)	34 (3.6)	0.661	16 (4.2)	27 (4.0)	1
COPD	39 (5.3)	19 (7.5)	0.26	23 (6.0)	35 (5.2)	0.671	10 (5.0)	50 (5.3)	1	23 (6.0)	35 (5.2)	0.671
Cancer	41 (5.6)	35 (13.8)	<0.001	18 (4.7)	58 (8.5)	0.026	12 (6.0)	70 (7.4)	0.611	18 (4.7)	58 (8.5)	0.026
Baseline drug use, n (%)												
Metformin	737 (100.0)	0 (0.0)	<0.001	352 (91.4)	343 (50.5)	<0.001	169 (84.9)	534 (56.1)	<0.001	352 (91.4)	343 (50.5)	<0.001

Sulphonylureas	352 (47.8)	27 (10.6)	<0.001	385 (100.0)	0 (0.0)	<0.001	123 (61.8)	240 (25.2)	<0.001	385 (100.0)	0 (0.0)	<0.001
DPP-4 inhibitors	169 (22.9)	28 (11.0)	<0.001	123 (31.9)	71 (10.5)	<0.001	199 (100.0)	0 (0.0)	<0.001	123 (31.9)	71 (10.5)	<0.001
Thiazolidine-diones	84 (11.4)	6 (2.4)	<0.001	58 (15.1)	31 (4.6)	<0.001	39 (19.6)	50 (5.3)	<0.001	58 (15.1)	31 (4.6)	<0.001
SGLT-2 inhibitors	70 (9.5)	8 (3.2)	0.002	37 (9.6)	41 (6.0)	0.043	41 (20.6)	34 (3.6)	<0.001	37 (9.6)	41 (6.0)	0.043
GLP1 receptor agonists	11 (1.5)	2 (0.8)	0.533	4 (1.0)	9 (1.3)	0.779	4 (2.0)	8 (0.8)	0.138	4 (1.0)	9 (1.3)	0.779
Insulin	208 (28.2)	49 (19.3)	0.007	120 (31.2)	129 (19.0)	<0.001	99 (49.7)	157 (16.5)	<0.001	120 (31.2)	129 (19.0)	<0.001
Statins	546 (74.1)	138 (54.3)	<0.001	294 (76.4)	379 (55.8)	<0.001	153 (76.9)	528 (55.5)	<0.001	294 (76.4)	379 (55.8)	<0.001
BP lowering drugs	473 (64.2)	165 (65.0)	0.882	250 (64.9)	381 (56.1)	0.006	129 (64.8)	529 (55.6)	0.02	250 (64.9)	381 (56.1)	0.006
RAAS inhibitors	440 (59.7)	126 (49.6)	0.006	248 (64.4)	303 (44.6)	<0.001	134 (67.3)	428 (45.0)	<0.001	248 (64.4)	303 (44.6)	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI, body mass index; BP, blood pressure; COPD, chronic obstructive airway disease; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HDL-C, high density-lipoprotein cholesterol; LDL-C, low density-lipoprotein cholesterol; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium glucose co-transporter-2

Table 2: Clinical outcome from COVID-19 according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
ICU admission, n (%)	108 (14.7)	43 (16.9)	0.442	79 (20.5)	79 (11.6)	<0.001	32 (16.1)	136 (14.3)	0.588	76 (27.8)	17 (2.7)	<0.001
Mechanical ventilation, n (%)	67 (9.1)	24 (9.5)	0.965	51 (13.2)	43 (6.3)	<0.001	22 (11.1)	78 (8.2)	0.244	51 (18.7)	4 (0.6)	<0.001
In-hospital death, n (%)	44 (6.0)	44 (17.3)	<0.001	35 (9.1)	47 (6.9)	0.248	18 (9.1)	71 (7.5)	0.538	32 (11.7)	22 (3.5)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	127 (17.2)	70 (27.6)	0.001	91 (23.6)	109 (16.1)	0.003	40 (20.1)	175 (18.4)	0.642	88 (32.2)	35 (5.6)	<0.001

DPP-4, dipeptidyl peptidase-4; ICU, intensive care unit

Table 3: Multivariate Cox regression for the association between baseline use of glucose lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission	0.53 (0.33, 0.86)	0.01	1.45 (0.96, 2.19)	0.074	0.45 (0.28, 0.74)	0.002	10.95 (5.5, 21.8)	<0.001
Mechanical ventilation	0.51 (0.27, 0.97)	0.041	1.35 (0.78, 2.36)	0.286	0.57 (0.29, 1.11)	0.098	21.99 (4.85, 99.6)	<0.001
In-hospital death	0.51 (0.27, 0.97)	0.039	2.42 (1.25, 4.7)	0.009	0.70 (0.35, 1.39)	0.304	2.86 (1.09, 7.48)	0.033
ICU admission, mechanical ventilation and/or in-hospital death	0.51 (0.34, 0.77)	0.001	1.55 (1.07, 2.24)	0.022	0.46 (0.29, 0.71)	<0.001	6.34 (3.72, 10.78)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), pre-admission use of other glucose-lowering drugs, statins, and RAAS inhibitors, and in-hospital use of other glucose-lowering drugs

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 1: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for comorbidities

Disease	ICD-9-CM Code	Description
Cardiovascular diseases		
Hypertension and hypertensive diseases	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive chronic kidney disease
	404	Hypertensive heart and chronic kidney disease
	405	Secondary hypertension
Coronary heart disease	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	412	Old myocardial infarction
	413	Angina pectoris
	414	Other forms of chronic ischemic heart disease
Heart failure	428	Heart failure
Chronic liver disease		
Chronic liver disease, liver failure, liver cirrhosis and complications	570	Chronic liver disease and cirrhosis
Diabetes mellitus		
Diabetes mellitus	250	Diabetes mellitus
Cancer		
Malignant neoplasm	140-149	Malignant neoplasm of lip, oral cavity, and pharynx
	150-159	Malignant neoplasm of digestive organs and peritoneum
	160-165	Malignant neoplasm of respiratory and intrathoracic organ
	170-176	Malignant neoplasm of bone, connective tissue, skin, and breast
	179-189	Malignant neoplasm of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites
	200-209	Malignant neoplasm of lymphatic and hematopoietic tissue
Cerebrovascular disease		
Cerebrovascular events	430	Subarachnoid haemorrhage
	431	Intracerebral haemorrhage
	432	Other and unspecified intracranial haemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
	438	Late effects of cerebrovascular disease
Chronic obstructive airway disease		
Chronic obstructive pulmonary disease and allied conditions	490-496	Chronic obstructive pulmonary disease and allied conditions
Kidney diseases		
Nephritis, nephrotic syndrome, and nephrosis	581	Nephrotic syndrome
	582	Chronic glomerulonephritis
	583	Nephritis and nephropathy not specified as acute or chronic
	585	Chronic kidney disease
	586	Renal failure, unspecified
	587	Renal sclerosis, unspecified
	588	Disorders resulting from impaired renal function
Others	403.1	Benign hypertensive renal disease
	403.9	Unspecified hypertensive renal disease

04.12404.1	Benign hypertensive heart and renal disease
3	Unspecified hypertensive heart and renal disease
404.1	Polycystic kidney, unspecified type
404.9	Polycystic kidney, autosomal dominant
753.12	Polycystic kidney, autosomal recessive
753.13	Gouty nephropathy
753.14	Postural proteinuria
274.1	Unspecified disorder of kidney and ureter
593.6	
593.9	

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Supplementary Table 2: Baseline clinical characteristics and in-hospital outcome of patients with and without type 2 diabetes admitted with COVID-19 in Hong Kong between January 2020 and February 2021

	Patients with diabetes		Patients without diabetes		
	Number (%) with available data		Number (%) with available data		p-value
Demographics					
Age, years	1220 (100.0)	65.3 (57.1, 73.1)	9839 (100.0)	44.6 (32.3, 58.6)	<0.001
Men, n (%)	1220 (100.0)	662 (54.3)	9839 (100.0)	4047 (47.0)	<0.001
Ex- or current smoker	1220 (100.0)	209 (17.1)	9839 (100.0)	868 (10.1)	0.001
Metabolic parameters					
Diabetes duration, years	1220 (100.0)	1.4 (0.3, 3.4)	-	-	-
BMI, kg/m^2	114 (9.3)	23.6 (21.5, 27.3)	598 (6.1)	23.5 (20.9, 26.5)	0.380
HbA1c, %	886 (72.6)	7.4 (6.6, 9.2)	1901 (19.3)	5.8 (5.4, 6.3)	<0.001
Comorbidities, n (%)					
Hypertension	1220 (100.0)	644 (52.8)	9839 (100.0)	815 (9.5)	<0.001
Coronary heart disease	1220 (100.0)	130 (10.7)	9839 (100.0)	148 (1.7)	<0.001
Heart failure	1220 (100.0)	44 (3.6)	9839 (100.0)	44 (0.5)	<0.001
Cerebrovascular disease	1220 (100.0)	111 (9.1)	9839 (100.0)	148 (1.7)	<0.001
Chronic kidney disease	1220 (100.0)	249 (20.4)	9839 (100.0)	235 (2.7)	<0.001

Chronic liver disease	1220 (100.0)	44 (3.6)	9839 (100.0)	44 (0.5)	<0.001
Chronic obstructive airway disease	1220 (100.0)	61 (5.0)	9839 (100.0)	235 (2.7)	<0.001
Cancer	1220 (100.0)	83 (6.8)	9839 (100.0)	180 (2.1)	<0.001
Baseline drug use, n (%)					
Metformin	1220 (100.0)	737 (60.4)	9839 (100.0)	0	<0.001
Sulphonylureas	1220 (100.0)	385 (31.6)	9839 (100.0)	0	<0.001
DPP-4 inhibitors	1220 (100.0)	199 (16.3)	9839 (100.0)	0	<0.001
Thiazolidinediones	1220 (100.0)	90 (7.4)	9839 (100.0)	0	<0.001
SGLT-2 inhibitors	1220 (100.0)	78 (6.4)	9839 (100.0)	0	<0.001
GLP1 receptor agonists	1220 (100.0)	13 (1.1)	9839 (100.0)	0	0.011
Insulin	1220 (100.0)	273 (22.4)	9839 (100.0)	0	<0.001
Statins	1220 (100.0)	709 (58.1)	9839 (100.0)	572 (6.6)	<0.001
Blood pressure lowering drugs	1220 (100.0)	691 (56.6)	9839 (100.0)	1108 (12.9)	<0.001
RAAS inhibitors	1220 (100.0)	590 (48.4)	9839 (100.0)	452 (5.2)	<0.001
In-hospital treatment, n (%)					
Oseltamivir	1220 (100.0)	16 (1.3)	9839 (100.0)	63 (0.7)	0.051
Ribavirin	1220 (100.0)	396 (32.5)	9839 (100.0)	1823 (21.2)	<0.001
Lopinavir-ritonavir	1220 (100.0)	335 (27.5)	9839 (100.0)	1542 (17.9)	<0.001

Interferon beta	1220 (100.0)	725 (59.4)	9839 (100.0)	2702 (31.3)	<0.001
Antibiotic therapy	1220 (100.0)	755 (61.9)	9839 (100.0)	2769 (32.1)	<0.001
Anti-fungal therapy	1220 (100.0)	124 (10.2)	9839 (100.0)	265 (3.1)	<0.001
Corticosteroid	1220 (100.0)	623 (51.1)	9839 (100.0)	1747 (20.3)	<0.001
Pulse methylprednisolone	1220 (100.0)	5 (0.4)	9839 (100.0)	7 (0.1)	0.011
Intravenous immune globulin	1220 (100.0)	6 (0.5)	9839 (100.0)	9 (0.1)	0.007
Clinical outcome, n (%)					
ICU admission	1220 (100.0)	187 (15.3)	9839 (100.0)	269 (3.1)	<0.001
Mechanical ventilation	1220 (100.0)	110 (9.0)	9839 (100.0)	142 (1.7)	<0.001
In-hospital death	1220 (100.0)	90 (7.4)	9839 (100.0)	105 (1.2)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death	1220 (100.0)	235 (19.3)	9839 (100.0)	340 (3.9)	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HDL, high density-lipoprotein; ICU, intensive care unit; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium glucose co-transporter-2

Supplementary Table 3: Laboratory results on admission and in-hospital treatment of patients with type 2 diabetes according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
Number	737	254		385	679		199	952		273	623	
Laboratory results on admission												
Random glucose, mmol/L	8.1 (6.4, 11.0)	7.1 (6.0, 9.0)	<0.001	8.7 (6.5, 12.1)	7.5 (6.1, 9.7)	<0.001	8.7 (6.6, 11.9)	8.0 (6.4, 11.2)	0.108	9.2 (6.6, 12.8)	7.6 (6.2, 9.5)	<0.001
Sodium, mmol/L	137.0 (134.0, 139.0)	138.0 (135.0, 140.0)	0.018	137.0 (134.0, 139.0)	138.0 (135.0, 140.0)	0.001	136.0 (134.0, 139.0)	137.0 (134.0, 139.0)	0.01	136.0 (133.0, 138.0)	138.0 (136.0, 140.0)	<0.001
Potassium, mmol/L	3.9 (3.6, 4.0)	3.8 (3.5, 4.2)	0.938	3.9 (3.6, 4.3)	3.8 (3.5, 4.2)	<0.001	4.0 (3.7, 4.4)	3.8 (3.5, 4.1)	<0.001	4.0 (3.6, 4.4)	3.8 (3.5, 4.1)	<0.001
Creatinine, µmol/L	77.7 (63.0, 98.0)	83.0 (66.7, 124.0)	<0.001	81.2 (66.0, 110.0)	75.0 (62.8, 95.0)	<0.001	90.0 (70.0, 138.0)	75.0 (62.4, 94.0)	<0.001	91.3 (71.0, 140.0)	72.0 (61.0, 88.1)	<0.001
Albumin, g/L	38.4 (35.0, 41.3)	37.5 (33.0, 41.0)	0.006	38.0 (34.1, 41.0)	38.7 (34.9, 41.7)	0.076	37.0 (33.3, 41.0)	38.7 (35.0, 41.7)	0.019	36.0 (32.0, 39.4)	39.7 (36.0, 42.1)	<0.001
Total bilirubin, µmol/L	7.9 (6.0, 10.2)	8.1 (6.0, 12.0)	0.164	7.8 (6.0, 10.0)	8.0 (5.8, 11.0)	0.580	7.5 (5.4, 10.4)	8.0 (6.0, 11.0)	0.116	8.0 (5.8, 10.6)	8.0 (6.0, 10.6)	0.604
ALP, U/L	67.3 (55.1, 82.0)	74.0 (60.0, 92.4)	<0.001	70.0 (57.0, 84.0)	69.0 (56.0, 84.0)	0.752	70.0 (57.0, 83.0)	69.1 (57.0, 84.8)	0.789	69.3 (55.0, 88.0)	70.0 (57.5, 83.5)	0.843

ALT, U/L	27.0 (18.0, 39.5)	25.1 (16.9, 37.0)	0.295	27.8 (20.0, 39.4)	26.1 (17.0, 41.0)	0.142	26.0 (17.8, 34.9)	27.0 (18.0, 41.7)	0.145	24.4 (17.0, 36.0)	28.6 (19.0, 42.8)	<0.001
LDH, U/L	213.0 (178.0, 277.0)	234.0 (192.0, 303.0)	0.002	214.0 (183.0, 281.0)	219.0 (180.0, 281.0)	0.720	216.0 (190.0, 277.0)	217.0 (181.0, 283.0)	0.505	246.0 (192.0, 362.0)	209.0 (175.0, 254.0)	<0.001
CRP, mg/dL	1.3 (0.4, 4.7)	1.2 (0.3, 5.0)	0.980	1.7 (0.4, 5.4)	1.1 (0.4, 3.9)	0.032	1.5 (0.4, 5.3)	1.3 (0.4, 4.6)	0.376	2.9 (0.5, 7.5)	0.8 (0.3, 2.6)	<0.001
ESR, mm/hour	38.6 (21.0, 65.2)	47.0 (22.5, 84.1)	0.060	43.0 (20.5, 68.0)	37.0 (21.0, 64.0)	0.844	45.6 (21.5, 72.5)	39.8 (21.0, 68.0)	0.622	46.0 (25.0, 80.0)	34.0 (18.5, 53.5)	0.002
Procalcitonin, ng/mL	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.039	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.299	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.308	0.1 (0.1, 0.3)	0.1 (0.1, 0.1)	<0.001
Haemoglobin, g/dL	13.0 (12.0, 14.0)	12.9 (11.6, 14.2)	0.225	12.9 (11.8, 13.9)	13.2 (12.1, 14.3)	0.008	12.9 (11.6, 13.9)	13.2 (12.1, 14.3)	0.003	12.9 (11.5, 14.0)	13.2 (12.1, 14.2)	0.002
White cell count, $x10^9$/L	5.7 (4.6, 7.2)	5.7 (4.4, 7.2)	0.611	5.8 (4.8, 7.4)	5.6 (4.4, 7.0)	0.002	6.1 (4.6, 7.4)	5.6 (4.5, 7.1)	0.031	6.1 (4.8, 8.0)	5.5 (4.4, 6.9)	<0.001
Lymphocyte count, $x10^9$/L	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	0.044	1.2 (0.9, 1.6)	1.2 (0.8, 1.5)	0.451	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	0.138	1.1 (0.8, 1.4)	1.2 (0.9, 1.7)	<0.001
Platelet count, $x10^9$/L	204.0 (160.0, 254.0)	188.0 (149.0, 234.0)	0.003	206.0 (161.0, 258.0)	197.0 (156.0, 243.0)	0.027	204.0 (159.0, 249.0)	198.0 (156.0, 250.0)	0.336	199.0 (151.0, 255.0)	207.0 (166.0, 260.0)	0.101
Prothrombin time, seconds	11.9 (11.3, 12.5)	12.1 (11.4, 12.9)	0.006	11.9 (11.4, 12.6)	11.9 (11.3, 12.5)	0.819	12.1 (11.5, 12.8)	11.9 (11.3, 12.5)	0.026	12.1 (11.5, 12.9)	11.8 (11.2, 12.3)	<0.001
In-hospital treatment, n (%)												

Oseltamivir	9 (1.22)	2 (0.79)	0.739	5.0 (1.3)	10.0 (1.5)	1	3.0 (1.5)	11.0 (1.2)	0.72	7.0 (2.6)	6.0 (1.0)	0.074
Ribavirin	236 (32.0)	84 (33.1)	0.818	125.0 (32.5)	221.0 (32.5)	1	75.0 (37.7)	290.0 (30.5)	0.056	103.0 (37.7)	185.0 (29.7)	0.022
Lopinavir-ritonavir	200 (27.1)	73 (28.7)	0.681	110.0 (28.6)	184.0 (27.1)	0.656	53.0 (26.6)	256.0 (26.9)	1	93.0 (34.1)	125.0 (20.1)	<0.001
Interferon beta	425 (57.7)	164 (64.6)	0.063	220.0 (57.1)	409.0 (60.2)	0.357	122.0 (61.3)	556.0 (58.4)	0.498	187.0 (68.5)	309.0 (49.6)	<0.001
Antibiotic therapy	444 (60.2)	176 (69.3)	0.013	246.0 (63.9)	405.0 (59.6)	0.193	125.0 (62.8)	582.0 (61.1)	0.717	210.0 (76.9)	273.0 (43.8)	<0.001
Anti-fungal therapy	80 (10.9)	26 (10.2)	0.875	52.0 (13.5)	58.0 (8.5)	0.014	32.0 (16.1)	81.0 (8.5)	0.002	47.0 (17.2)	40.0 (6.4)	<0.001
Corticosteroid	367 (49.8)	142 (55.9)	0.108	201.0 (52.2)	330.0 (48.6)	0.286	108.0 (54.3)	475.0 (49.9)	0.296	168.0 (61.5)	203.0 (32.6)	<0.001
Pulse methylprednisolone	2 (0.27)	1 (0.39)	1	1.0 (0.3)	4.0 (0.6)	0.659	0.0 (0.0)	4.0 (0.4)	1	1.0 (0.4)	1.0 (0.2)	0.517
IVIG	2 (0.27)	2 (0.79)	0.272	2.0 (0.5)	2.0 (0.3)	0.623	0.0 (0.0)	5.0 (0.5)	0.594	2.0 (0.7)	0.0 (0.0)	0.093

Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables

ALP, alkaline phosphatase; ALT, alanine transaminase; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; ESR, erythrocyte sedimentation rate; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase

Supplementary Table 4: Incidence rate, per 1,000 person-year, of clinical outcome from COVID-19 according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulfonylureas			DPP4-inhibitors			Insulin		
	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value	Users	Non-users	p-value
ICU admission	4176.3	4063.2	0.879	6185.6	3042.6	<0.001	4146.0	3958.9	0.814	7525.9	783.6	<0.001
Mechanical ventilation	2101.5	1885.2	0.648	2894.0	1437.5	0.001	2287.6	1839.8	0.366	3519.7	179.8	<0.001
In-hospital death	1258.8	2946.5	<0.001	1673.1	1454.3	0.530	1561.2	1521.9	0.923	1734.8	977.2	0.036
ICU admission, mechanical ventilation and/or in-hospital death	4914.1	6633.4	0.043	7134.4	4202.9	<0.001	5186.2	5100.3	0.924	8728.4	1615.4	<0.001

DPP-4, dipeptidyl peptidase-4; ICU, intensive care unit

Supplementary Table 5: Multivariate Cox regression with propensity score weighting for the association between baseline use of glucose-lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission, n (%)	0.51 (0.30, 0.86)	0.012	1.42 (0.90, 2.25)	0.131	0.46 (0.28, 0.76)	0.002	9.79 (4.26, 22.50)	<0.001
Mechanical ventilation, n (%)	0.29 (0.12, 0.72)	0.008	1.30 (0.70, 2.44)	0.405	0.42 (0.18, 0.98)	0.044	21.21 (4.40, 102.31)	<0.001
In-hospital death, n (%)	0.45 (0.23, 0.89)	0.022	2.87 (1.40, 5.88)	0.004	0.78 (0.38, 1.59)	0.487	2.86 (0.81, 10.13)	0.103
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	0.53 (0.35, 0.81)	0.003	1.55 (1.02, 2.34)	0.04	0.48 (0.30, 0.76)	0.002	5.90 (3.41, 10.20)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), baseline use of other glucose-lowering drugs, statins and RAAS inhibitors, in-hospital use of other glucose-lowering drugs, and propensity score

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 6: Multivariate Cox regression for the association between baseline use of glucose-lowering drugs and clinical outcome after excluding patients who were identified as having diabetes based on a single fasting plasma glucose (n=25)

	Metformin		Sulfonylureas		DPP4-inhibitors		Insulin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
ICU admission	0.58 (0.35, 0.97)	0.039	1.48 (0.97, 2.25)	0.067	0.48 (0.29, 0.79)	0.004	12.49 (5.85, 26.68)	<0.001
Mechanical ventilation	0.49 (0.25, 0.97)	0.039	1.36 (0.77, 2.39)	0.286	0.62 (0.32, 1.20)	0.153	34.23 (4.40, 266.34)	<0.001
In-hospital death	0.47 (0.25, 0.90)	0.023	2.36 (1.21, 4.58)	0.011	0.70 (0.35, 1.39)	0.303	3.28 (1.21, 8.91)	0.020
ICU admission, mechanical ventilation and/or in-hospital death	0.53 (0.35, 0.82)	0.004	1.56 (1.07, 2.28)	0.020	0.47 (0.30, 0.74)	<0.001	6.44 (3.71, 11.20)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), baseline use of other glucose-lowering drugs, statins and RAAS inhibitors, and in-hospital use of other glucose-lowering drugs

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; ICU, intensive care unit; RAAS, renin-angiotensin-aldosterone system

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10, 25-26
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.